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Diabetic Retinopathy In Patients With Type 2 Diabetes: Aspects Of Early Diagnosis, Treatment And Prediction Of The Outcome Of The Disease

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ABSTRACT

In this review, the authors performed an overview of the literature on early diagnosis, treatment and methods for predicting the outcomes of the disease. According to regional endocrinological dispensaries, for 2020 registered SD for RUZ 277 926., Of these, type 1 type 18178, SD 2 type 259,748 patients. At the same time, the number of patients with DR was 2020 g of 83,632 persons, of which 73690 persons with di type 2. The real number of patients exceeds a registered 10 times, over the past 18 years, the number of patients with a rope in Uzbekistan increased by 2.4 times (according to the Ministry of Health of RUZ).

The prevalence of others among patients of the CD is 10-90%, according to some specialists, up to 97-98.5%. For example, the frequency of development dr in India is lower than among Europeans and Americans, and among the black population more frequent than among the white. According to the WHO research group, it was revealed that the highest frequency of DR was detected in Oklahoma (76.4%), Zagreb (73.1%) and Hong Kong (58.1%). The lowest frequency was observed in Tokyo (29.7%). The prevalence of DR in patients in China amounted to 47.4%, and the frequency of DR in Poland was 31.4%.

KEYWORDS

Type 2 diabetes, diabetic retinopathy, early diagnosis issues.

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INTRODUCTION

Relevance. According to scientific research, over the past decades, type 2 diabetes mellitus (DM 2), along with cardiovascular and oncological diseases, has become an increasingly common pathology and by now has acquired the scale of a "non-infectious epidemic" [1, 2, 7;].

In addition, type 2 diabetes is one of the common causes of disability and mortality, which is due to late complications of the disease, which include microangiopathy - damage to capillaries, arterioles and venules, clinically manifested in the form of neuropathy, retinopathy and nephropathy. Macroangiopathy - damage to large and medium-sized vessels leads to myocardial infarction, stroke and gangrene of the lower extremities. In addition, in the pathogenesis of neuropathy, a significant place is given to the primary damage to the vessels involved in the blood supply to the peripheral parts of the nervous system [51, 3, 7].

The United Kingdom Prospective Diabetes Study (UKPDS) and the Chronic Complications of Diabetes Study (DCCT) are two landmark studies that have shown conclusively that tight glycemic control has a positive effect on microvascular endpoints [24,25].

The results of the well-known 40-year prospective study of diabetes mellitus 2 according to UKPDS showed that in patients with type 2 diabetes, a decrease in the average annual level of glycated haemoglobin by 1% reduces the likelihood of death from diabetes complications by 21%. At the same time, the risk of developing microangiopathies decreases by 37%, the risk of myocardial infarction - by 14%, stroke - by 12%, heart failure - by 16% [44; 46]. Follow-up of patients in the intensive glycemic control group for ten years after the completion of the study proved the feasibility of achieving optimal glycemic control in patients with type 2 diabetes as early as possible to reduce the risk of myocardial infarction and overall mortality [27, 32, 33, 43].

The Diabetes Chronic Complications Trial (DCCT) studies have shown convincingly that for every 1% increase in HbA1c, the risk of progression of DR increases by 50%. Conversely, with a decrease in HbA1c for every 1%, the risk of DR progression decreases by 43–45%, and there is a decrease in microvascular complications by 25–35%. A 1.5% decrease in HbA1c leads to a 24–33% decrease in DR progression [DCCT-1993]. Other studies indicate that the risk of developing proliferative DR is 22 times higher in patients with HbA1c levels> 10% [4].

A sample of a multinational WHO study of type 2 diabetes patients aged 35-55 years, depending on the type of diabetes, showed that the prevalence of DR in type 2 diabetes patients is 11.4-61.6% of the total number of patients examined [36], and the incidence of retinopathy in diabetes Type 1 was higher than type 2 diabetes in Switzerland, Berlin, Tokyo and Havana [39].

Similar data were found in a study in Albania, where the incidence of DR among patients with type 1 diabetes was 43%, and among patients with type 2 diabetes - 22% [47].

In connection with the above, the purpose of our work is a review of works devoted to a comprehensive clinical and epidemiological study of early diagnosis, treatment and prognosis of disease outcomes.

The prevalence of DR in patients with diabetes. It has been established that DR occurs in all age groups of patients with

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diabetes [35], but the most frequent and severe fundus lesions are observed at the age of 48-60, ie. in the elderly [36]. Despite this, recently, DR is more common at a younger age and takes on a rather severe clinical course [21]. In patients with type 2 diabetes with a disease duration of up to 2 years, DR is found in 20% of cases, with a duration of more than 10 years - in 75-85% of patients [4]. 5-7 years after the onset of the disease, clinically definable symptoms of DR are found in 15-20% of cases, after 10 years - in 50-60%, after 15-20 years - in 80%, and after 30 years - in almost all patients [39]. In type 2 diabetes, due to late diagnosis, the signs of DR are detected already at diagnosis of diabetes in 15–40% of cases, since it is usually impossible to establish the exact time of the onset of the disease [4, 24; 33]. The incidence of proliferative DR is: with a duration of diabetes up to 10 years - 3-5%, 10-15 years - 20-30%, 20-30 years - 60%, with a duration of more than 35-40 years, the frequency of proliferative retinopathy progressively decreases due to with high mortality due to the duration of diabetes, and if DR has not yet developed, the likelihood of its occurrence is low [35].

According to the data of regional endocrinological dispensaries, in 2020, diabetes was registered in RUz 277 926, of which type 1 diabetes 18178, type 2 diabetes 259 748 patients. At the same time, the number of patients with DR was 83,632 in 2020, of which 73,690 were with type 2 diabetes. The real number of patients exceeds the registered one by 10 times, over the past 18 years the number of patients with diabetes in terms of accessibility in Uzbekistan has increased 2.4 times (according to the Ministry of Health of the Republic of Uzbekistan)

LITERATURE REVIEW

As can be seen from the above data, epidemiological studies are very relevant and are carried out to this day all over the world. However, there are not enough works devoted to the study of early diagnosis, prediction and treatment of late complications of diabetes with the use of modern high technologies in our Republic [10].

Yangieva N.R. (1997) carried out one of the first epidemiological studies to study the prevalence of one of the late complications of diabetes - diabetic retinopathy, later (2019) Kamilov Kh.M. and Normatova N.M. studied the deeper epidemiological aspects of diabetic retinopathy in the republic [12].

Endocrinologists at the Republican Scientific and Practical Center for Endocrinology carried out an epidemiological study of POSD among adults F.A. Khaidarova. (1998). So, the work of Kayumova D.T. (2008) and Nabieva I.F. [41] summarized the results of studies only in newly diagnosed patients with type 2 diabetes, and the clinical manifestations of DES in this case.

In the literature, there are numerous works on the identification and prevalence of late complications of diabetes mellitus (POSD) among patients with diabetes in rural areas [9; 18].

One of such works in our republic is the work of Ikramova F.A., who, using the screening method as an example of the Bukhara region, studied the prevalence of one of the specific complications of diabetes mellitus, in particular, microalbuminuria (MAU) in patients with type 2 diabetes. Population studies of mortality among patients with diabetes were carried out in many European countries, in

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Japan, the USA, in Asia [31; 38; 50] and Russia [11; 14].

The structure of mortality in diabetes was studied in Tashkent in the period from 1997-2002 by B.Kh. Shagazatova (2004), as well as since the establishment of the National Register in the Republic of Uzbekistan both in children (2001) [1] and in adults (2010), domestic scientists have been analysing the mortality rate of patients with diabetes mellitus.

MATERIALS AND METHODS

With regard to such an important aspect of diabetes as the prevalence of its complications, according to some authors, it is known that the incidence of diabetes complications varies depending on the ethnicity of patients suffering from this disease [38]. The prevalence of DR among patients with diabetes is 10-90% [4; 13], according to some experts - up to 97- 98.5% [37]. For example, the incidence of DR in India is lower than among Europeans and Americans [41; 42], and among the African population, it is more frequent than among Caucasian patients [4; 39]. According to the WHO research group, it was found that the highest incidence of DR was found in Oklahoma (76.4%), Zagreb (73.1%) and Hong Kong (58.1%), the lowest incidence was observed in Tokyo (29.7 %). The prevalence of DR in patients with diabetes in China was 47.4%, and the incidence of DR in Poland was 31.4% [29; 38; 39]. In Ukraine, over the past decades, the prevalence of DR has increased more than 10 times. If in 1975 the level of visits to an ophthalmologist for DR was 1.2 per 10 thousand of the population, then in 1991 this figure increased to 8.4, and in 2001 it reached 15.2 [4].

In Georgia, the prevalence of DR in newly diagnosed patients with type 2 diabetes was 16.4% (non-proliferative form in 14%; pre proliferative form in 1.1%; proliferative form in 1.4%, cataract was detected in 20.8%, blindness - 0.8%) [16]. In Uzbekistan, the frequency of DR in patients with diabetes, according to the 1998 data of F.A. Khaidarova, was 79.1% [22].

When studying the prevalence of DR in several regions of Russia, it was revealed: in the Leningrad region up to 52.4%, in the Omsk region up to 38.6%, in Novosibirsk - 53.6% [12; 20], in Novokuznetsk the DR frequency was 49.1% [5], in Ryazan 75% and 86.3%, respectively, with type 1 and type 2 diabetes [8], in the Tyumen region in patients with type 2 diabetes, 39.7 % [19]. The frequency of types of diabetes in patients with DR in some cities of Russia was different, for example, the incidence of DR in Ryazan in patients with type 1 diabetes was 75%, but with type 2 diabetes 86.3% [8], while in Tyumen this ratio was 72, 7% and 39.4%, respectively [19].

As you know, the most severe form of eye damage is proliferative DR (PDD).

At the same time, there is an uncontrollable growth of pathological tissue structures in the retina, which appear in about 10-40% of all patients with diabetes, which, despite treatment, quickly and steadily leads to loss of vision in 2% of cases and in 10% of cases - to severe visual impairment ... [4; 17; 23].

PDD in type 2 diabetes develops less frequently than in type 1 diabetes. The proliferative form is distributed approximately the same in both sexes. The peak of its frequency falls at the age of 60 years, after which the frequency decreases [4; 6; 35]. The data on the prevalence of DN from the WHO are consistent

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with the data on the high frequency of DN in Asia and in the American Indians. In all published data on the study of the incidence rates of retinopathy, the incidence rate of PDD in type 1 diabetes is more than double that in type 2 diabetes. Proliferative DR in type 2 diabetes develops less frequently than in type 1 diabetes. Thus, 20 years after the onset of diabetes, proliferative DR is found in 60% of patients with type 1 diabetes and only in 20% of patients with type 2 diabetes [4; 16].

Early diagnosis of DR. Although DR remains the leading cause of vision loss, the past decade has brought significant advances in the diagnosis and treatment of this common complication of diabetes, thanks to the advent of high-tech ophthalmic equipment. First, the OCT (optical coherence tomography) equipment that appeared at the beginning of the 21st century makes it possible to obtain non-invasive images of the retina, in particular, the macula, with a very high resolution, which makes it easier to visualize and monitor the effectiveness of the treatment of diabetic macular oedema. In addition, recent advances in understanding the pathophysiology of DR, in particular the key role of cytokines such as vascular endothelial growth factor (VEGF), have led to the development of anti-VEGF antibodies for intraocular use. Anti-VEGF therapy has largely replaced laser photocoagulation for the treatment of diabetic macular oedema. The benefits of intravitreal anti-VEGF in diabetic macular oedema have been proven in numerous large randomized controlled trials. At the same time, the role of inflammation in DR has been recognized and several anti-inflammatory agents, mainly steroid-based, for intravitreal treatment, are effective. Despite recent scientific advances, strict systemic glycemic control, which is the cornerstone of DR treatment, can reduce the incidence and prevalence of ocular complications, including [32,28].

The results of numerous studies have shown that at the time of the establishment of type 2 diabetes, patients already have microvascular complications in the fundus [32; 36]. With an increase in the duration of diabetes, the prevalence of MAU and PU changes [10; 19; 21]. After 5-7 years from the onset of the disease, clinically definable symptoms of DR are found in 15-20% of cases, after 10 years - in 50-60%, after 15-20 years - in 80%, and after 30 years - in almost 100% of patients [33]. In type 2 diabetes, due to late diagnosis, signs of DR are detected already upon diagnosis of diabetes in 15–40% of cases, since it is usually not possible to establish the exact time of onset of the disease [4].

The incidence of proliferative DR is: with a duration of diabetes up to 10 years - 3-5%, 10-15 years - 20-30%, 20-30 years - 60%, with a duration of more than 35-40 years, the incidence of proliferative DR progressively decreases in associated with high mortality caused by the duration of diabetes, and if DR has not yet developed, the likelihood of its occurrence is low [35].

DR treatment issues. Numerous studies of aspects of the development of DR, which covered such countries as England, Australia, Germany, Spain in 2016, showed that DR is the most common complication of diabetes mellitus and remains the leading cause of vision loss worldwide. Its aetiology and pathology have been widely studied for half a century, however, there are few options for diagnosis and standard treatment of diabetes mellitus complicated by DR [26].

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New treatments (for example, intravitreal inhibitors of vascular endothelial growth factor "anti-VEGF"), widely used worldwide for the treatment of diabetic macular oedema (DMO), are not always successful in 50% of patients. In addition, for patients with proliferative DR (PDD), laser photocoagulation remains the main therapy, even though inherently this procedure is destructive. The authors emphasize that although significant advances have been made in treatment, there is still an urgent need for a better understanding of the underlying mechanisms to develop reliable tools for identifying patients at high risk of complications and for effective intervention before visual impairment.

Complications arising in the diabetic retina have been discussed for many decades using descriptive and experimental approaches based on clinical studies of patients, pathological material, experiments on models and various in vitro systems.

Research has also accumulated a wealth of knowledge about the underlying molecular mechanisms and key pathogenic processes that cause these abnormalities in the retina in diabetes. Despite these advances, treatments for DR are still limited, and currently, only treatments for advanced disease are available [33, 36, 41].

Particular attention is paid to the issues of understanding complex neuronal, glial and microvascular anomalies, which gradually disrupt the function of the retina in the initial stages of diabetes mellitus 2. Based on a deep understanding of the cellular and molecular pathology underlying DR, researchers are striving to develop effective therapeutic options that can act in both the early and advanced stages of the disease. It is known that chronic hyperglycemia disrupts the internal and external blood-barrier barrier of the retina, which leads to increased regulation of vascular endothelial growth factor (VEGF). In randomized clinical trials, intravitreal anti-vascular endothelial growth factor or anti-VEGF agents, including ranibizumab, bevacizumab, and aflibercept, are superior to macular laser in the treatment of clinically significant diabetic macular oedema. The READ-2, RISE / RIDE, and RESTORE studies showed ranibizumab was superior to the macular laser, while the BOLT study demonstrated the superiority of bevacizumab over laser. DRCR.net Protocol T results showed that aflibercept, bevacizumab, and ranibizumab, when injected into the vitreous humour, were effective in reducing retinal thickness secondary to diabetic oedema and in improving vision. When the vision was 20/40 or higher, the visual improvement was equivalent. At 20/50 or worse vision, aflibercept was more effective at improving vision. Intravitreal anti-VEGF therapy can be economically and ethically burdensome for the patient, often requiring monthly doctor visits. In this regard, it is especially important to develop a therapy strategy that allows you to increase the duration of remission and expand the interval between treatment courses [30].

According to the authors from France, the changes in non-perfusion of the retina (NP) after anti-vascular endothelial growth factor (VEGF) therapy in diabetic macular oedema (DME) were assessed using 2 different imaging methods: open-source OCT angiography (SS-WF OCTA) and fluorescence angiography (UWF FA). Vascular or capillary reperfusion was not detected in NP regions using two imaging modalities, UWF FA and SS-WF OCTA, in DR eyes after 3 anti-VEGF injections. The detection

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rate of NP areas was higher with SS-WF OCTA than with UWF FA [27]. Given the global increase in the incidence of type 2 diabetes and complications such as DR, ophthalmologists need to know about these new agents and their effect on diabetic retinopathy and diabetic macular oedema, according to a multicenter study in Australia [40].

A review of the current literature by these authors showed that thiazolidinediones and antihyperglycemic agents have been reported to have a positive or neutral effect on diabetic ocular complications. Thiazolidinediones (pioglitazone is the only one currently available) have been associated with the onset or worsening of diabetic macular oedema, although the incidence is considered low. Glucagon-like peptide 1 (GLP1) agonists (incretins) are generally useful, with the exception of Semaglutide, which is associated with an increased complication rate of diabetic retinopathy. These results have implications for the choice of antihyperglycemic agents for patients with DR or macular oedema. The authors stressed that more research is needed to determine if the reported benefits are dependent on the effects of glycemic control. The early deterioration of tightly controlled retinopathy should also be noted in the interpretation of future studies [40].

According to the authors from the USA, a new approach to the prevention and treatment of DR at an early stage before the onset of serious visual impairment is presented [45].

The authors note that this approach involves two main steps. The first step is to understand the mechanisms of visual impairment and classify based on pathophysiological adaptations, and not based on the presence of advanced pathological lesions, as defined in modern clinical practice. The second step is to develop patient-specific molecular DR diagnoses so that patients can be treated based on their characteristics, a process similar to individual diagnosis and treatment of cancer patients. This step is illustrated by an analysis of the vitreous body, which reveals signs of neuroretinal degeneration and inflammation, as well as the process of germination of new vessels.

Predicting disease outcomes. The DCCT studies have shown that for every 1% increase in HbA1c, the risk of progression of DR increases by 50%. Conversely, with a decrease in HbA1c by every 1%, the risk of DR progression decreases by 43–45% and a decrease in microvascular complications by 25–35% is noted.

A 1.5% decrease in HbA1c leads to a 24–33% decrease in DR progression [DCCT-1993]. Other studies note that the risk of developing proliferative DR is 22 times higher in patients with HbA1c levels> 10% [4; 15].

RESULTS AND DISCUSSION

The UKPDS results showed that in type 2 diabetes patients, a 1% decrease in the average annual level of glycated haemoglobin reduces the likelihood of death from diabetes complications by 21%. At the same time, the risk of developing microangiopathies decreases by 37%, the risk of myocardial infarction - by 14%, stroke - by 12%, heart failure - by 16% [44; 46].

Regardless of the type of diabetes, the development of retinopathy is promoted by the decompensation of diabetes, irregular control of blood sugar levels, from the content of glycated haemoglobin in the blood and neglect of measures for its correction [4; 39;

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47]. Similar studies have been carried out in several other countries [35].

The role of smoking in the development of DR is disputed [39]. Many authors distinguish overweight and intoxication among the risk factors influencing the frequency of DR, as well [35].

A WHO study showed that smokers have a lower risk of any type of retinopathy and disease progression to PDD than nonsmokers, but when such parameter as fasting plasma sugar is included in the analysis, this advantage sounds unfounded [38].

It has been established that DR occurs in all age groups of patients with diabetes [35; 44], but the most frequent and severe fundus lesions are observed at the age of 48-60, ie. in the elderly [36; 45]. Despite this, recently, DR is more common at a younger age and has a rather severe clinical course [21].

Saudi Arabian authors Abdul Hamid Al Ghamdi et al. [24] performed a progression analysis of DR and data for a systematic review were collected from published studies through PubMed and Medline. These studies discussed clinical predictors of the progression of diabetic retinopathy (DR). The keywords commonly used were DR, diabetes mellitus, systolic blood pressure, haemoglobin, and albuminuria. According to them, poor glycemic control, systemic hypertension, duration of diabetes, dyslipidemia and microalbuminuria are the main risk factors for the development and progression of diabetic retinopathy. Increased aortic stiffness has been identified as a predictive marker for DR and peripheral neuropathy.

Chinese authors studied the effect of hypoxia inducing factor (HIF) -1α on the expression of vascular endothelial growth factor (VEGF) and angiogenesis in DR [2]. 8-week-old healthy SD rats were used for the experiments. Under systemic anaesthesia, control rats were injected with saline in the vitreous body of the left eye (control group A) and 2 μl of oligonucleotides (ASODN) (10 μmol / L) in the right eye (control group B). Model rats were injected with saline in the left eye (model group A) and 2 μl ASODN (10 μmol / L) in the right eye (model group B). Rats were injected intraocularly with HIF-1α ASODN for 2, 4 and 6 weeks (A1, A2, A3, B1, B2, B3, respectively). Retinal vascular development was monitored by ADP staining. Vascular endothelial cells penetrating into the inner membrane of the retina were counted.

Immunohistochemistry was used to detect the expression of VEGF and HIF-1α proteins in the retina. Severe angiogenesis and hyperplasia were found in the model A group.

Relatively fewer newly formed vessels were shown in model group B. The authors concluded that retinal angiogenesis is closely associated with increased levels of HIF-1α. Inhibition of HIF-1α inhibited VEGF expression and inhibited angiogenesis over time. This provided new ideas for the treatment of DR.

The American authors performed the original study on Müllerian glia (MG), which are the main supporting cells of the retina that are involved in the metabolism, functioning, maintenance and protection of the retina. In DMG, it modulates vascular function and neuronal integrity by regulating the production of angiogenic and trophic factors. In this work, the authors distinguished the role and mechanism of MG modulated vascular function through the production of vascular endothelial growth factor (VEGF) and the study of MG

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viability mediated by VEGF signalling and nervous protection in diabetic patients in animals [48].

A study at several centres in the United States and China in 2020 showed that circulating miR-15b (miR-microribonucleic acid) is directly associated with VEGF compared to other miRs in patients with proliferative DR (PDD) [49].

They found a significant inverse relationship between low levels of miR-15b and high levels of VEGF in patients with PDD compared to the T2DM or NPDR groups. They found that miR-15b regulates VEGF expression by targeting 3'-untranslated regions to inhibit its transcription. Similarly, miR-15b overexpression inhibited vascular abnormalities in vivo in diabetic rats by inhibiting endothelial tube formation and VEGF expression. Thus, the performed review of the literature showed a variety of aspects on the pathogenesis, diagnosis, and treatment of DR. Despite many scientific advances, treatment standards for DR are still insufficiently pathogenetically developed and justified, especially in the early stages of the disease.

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