Glaucoma and Diabetic Retinopathy in patients with diabetes mellitus type 2. Review.

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SUMMARY

Glaucoma and diabetic retinopathy (DR) are the most frequent reasons of visual loss and disability. Combination of glaucoma and DR causes worse prognosis. Similarity of pathogenetic mechanisms of DR and glaucoma allows consideration of more frequent development of primary open-angle glaucoma among patients suffering diabetes mellitus. To reveal these diseases at the earliest stages is one of the most difficult ophthalmological problems. The contemporary methods of DR and glaucoma diagnostics are optical coherence tomography and Heidelberg retina tomography. They give an opportunity to estimate the dynamics of pathological process and the efficiency of surgical and pharmacological treatment. Optical scanning of an optic disk and peripapillary retina gives a chance to estimate up to 20 morphometric parameters. Determination of retinal nerve fiber layer (RNFL) thickness in peripapillary zone reflects a condition of nerve fibers and extent of their defeat. It is shown that in glaucoma there is a thinning of RNFL and a neuroretinal rim. In early diagnostics of glaucoma the parameters of optic disk characterizing neuroretinal rim are considered the most informative. OCT considerably expands diagnostic research possibilities of structural and morphological retinal changes in a macular zone in patients with DR and DME. Measurement of retinal thickness in macular area is a key point in diagnostics and tactics of treatment. The standard method of DR therapy is retinal laser coagulation. However, laser photocoagulation as monotherapy is not effective enough in patients with diffuse and cystoid macular edema. It is more reasonable to use retinal laser photocoagulation in combination with antiangiogenic therapy for treatment of the diabetic macular edema (DME) and DR. The special emphasis is put on development of treatment algorithm of combination of glaucoma and diabetic retinopathy. Therapy of neovascular glaucoma in patients with diabetes mellitus type 2 is a complex problem. Such patients traditionally get panretinal laser photocoagulation. Recently anti-VEGF-agents are used as additional therapy of neovascular glaucoma. However, nowadays the influence of antiangiogenic treatment on dynamics of clinical and morphological parameters in patients with the combined pathology is insufficiently investigated.

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Diabetes represents a serious clinical and social problem in connection with prevalence and high level of disability of patients. The World Health Organization (WHO) in 2013 speaks about pandemic of diabetes in the world. Over the last 10 years the frequency of incidence of diabetes increased more than twice. By 2013 the number of such patients in the world was 371 million people, in Russia — 8 million people [1]. Experts of the International diabetic association (IDF) predict growth of number of patients with diabetes, which will increase to 552 million people by 2030 [2]. Diabetes is characterized by a complex of negative consequences caused, first of all, by vascular complications. One of them is diabetic retinopathy (DR). Today DR takes a main place among the reasons leading to loss of eyesight in population of economically developed countries. DR is observed in 90% of patients with diabetes mellitus and mostly manifests in 5-10 years from an onset of the illness. Development of DR contributes to occurrence of other types of eye pathology, creating mixed forms of diseases dif-

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ficult in diagnostic and therapeutic aspect. Quite often DR is combined with glaucoma which has great medical and social value in view of prevalence and weight of outcomes of a disease.

For the last decades significant increase of glaucoma incidence is noted both in Russia and around the world. According to Quigley (2011) about 60 million people in the world suffer from glaucoma, and its share in blindness and low vision makes 29% [3,4]. It is known that patients with diabetes mellitus type 2 have glaucoma 4-5 times more often than in general population, and patients with diabetes lasting more than 12-15 years with a proliferative diabetic retinopathy belong to a group of increased risk [5,6]. According to classification by E. Kohner and M. Porta in 1991 accepted by WHO, secondary neovascular glaucoma is considered a final stage of diabetic damage of an eye, taking the second place in the reasons of irreversible blindness [7]. The combination of glaucoma and DR increases severity of diseases and does the prognosis less positive.

The reasons of frequent association of DR and glaucoma remain insufficiently clear. At the same time there are bases to assume existence of the general pathogenetic links connected with vascular dysfunction.

The basis of metabolic diabetic defeat of a vascular wall is a violation of glycosaminoglycan exchange, consisting in accumulation of products of a sorbitol (polyol) cycle of glucose exchange. Surplus of glycozylation products leads to an increase of vascular permeability, stimulates a tissue expression of endotelin-1, pro-inflammatory cytokines (IL-1, IL-6, FNO-A), growth factors and proteins of extracellular matrix [7]. Realization of similar pathophysiological reactions provokes ischemic tissue damage. The local hypoxia in a retina induces production of hypoxia inducible factor (HIF-1 alpha) [8,9]. Endothelial cells start producing actively a vascular endothelial growth factor VEGF-A, playing a key role in stimulation of endothelial proliferation, its prothrombogenic activity, regulation of thrombogenic microvascular resistance and permeability [10]. The raised expression of angiogenic factors launches a neovascularization cascade with formation of neogenic vessels in retina, iris, trabecula and in corner of an anterior chamber [7,11]. New vascular elements are characterized by fragility and the raised transudation of plasma. Because of inferiority of such vascular structures there is a blocking of ways of aqueous humor outflow by plasma proteins, promoting an increase of intraocular pressure and development of secondary neovascular glaucoma [12].

It is considered that in the course of violation of aqueous humor outflow in diabetes the key role is played by degenerated processes in the iridocorneal complex, caused by diabetic defeat: iris dystrophy, destruction of a pupillary border, endothelial thickening and proliferation of a back wall of Schlemm's canal, sclerotic changes in trabecular network [7]. During a number of the researches conducted by in vitro with use of culture of trabecular network cells, it was revealed that in hyperglycemia conditions there is a hyperproduction of the main components of extracellular matrix — fibronectin, collagen type 4 and lamimin. It can lead to a decrease in permeability of a trabecular network and, finally, to development of POAG in patients with diabetes. Thickening of a vascular basal membrane and induction of an abnormal production of its components are consequences of glucose mediated expression of extracellular matrix. As a result of these changes the permeability of retinal vessels increases being a basis of diabetic retinopathy development.

In confirmation of the vascular concept of glaucoma damage (S. Hayreh 1978, G. Spaeth 1977, Bunin A. Ya. 1971) [13] there is an active expression of hypoxia inducible factor (HIF-1alpha) in ganglionar nerve cells and in optic nerve head in POAG [8]. Hypoxia in its turn induces production of growth factors VEGF-A and TGF-beta (transforming growth factor) which cause degenerated changes in extracellular matrix of lamina cribrosa of optic nerve head. These changes weaken its basic functions. Tolerance of an optic nerve to ophthalmotonus decreases. As a result of mechanical action of raised IOP, the deformation of a basic framework strengthens, causing collapse of basic astroglial tissue and vessels in the damaged zone. Over time, deformation of a lamina cribrosa progresses, infringement of nerve fiber bunches in the pores of a lamina cribrosa arise, axonal transport is damaged [3].

Dyslipidemia and oxidative stress are considered the factors involved in pathogenesis both in diabetes and POAG. The oxidative stress is accompanied by balance violation between antioxidant system and level of free radicals (oxidizers) in favor of the last, having destructive effect on tissue structures [14]. Overproduction of nitric oxide takes a special place in mechanisms of local autoregulation of bloodstream and is revealed in patients with DR and POAG [8]. In hypoxia an activation of free radical processes occurs. They consequently lead to transformation of nitric axide into peroxynitrite, damaging cells by nitridation of proteins and DNA [15]. It is proved that strengthening of oxidative stress in DR promotes an increase of expression of a vascular endothelial factor VEGF-A [16]. According to D. Anderson (1970) violation of concentration of vasoactive agents in combination with raised IOP, is a key point in pathogenesis of glaucoma atrophy [13]. In the combined pathology strengthening of oxidative tissue damage should be expected.

Similarity of pathogenetic mechanisms of development of DR and glaucoma allows assumption of possibility of more frequent POAG among the patients with diabetes.

The problem of early detection of these diseases is one of the most difficult in ophthalmology. However, traditional methods of diagnostics and monitoring such as tonometry, biomicroscopy, ophthalmoscopy and fluorescent angiography are all qualitative and based on subjective assessment of a doctor and do not give full information about

pathological process. Modern ways of diagnostics of glaucoma and DR are objective research methods such as optical coherence tomography (OCT) and Heidelberg retinotomography (HRT).

OCT was developed in 1991 in the Michigan Institute of Technology (MIT) and since 1997 it has been used actively in clinical practice [17]. This method of investigation allows visualization of pathological changes of a retina and an optic nerve in real time. It is also contributes sufficiently to diagnostic opportunities of angiographic researches. By means of OCT it is possible to estimate a condition of retina in macular area, to measure its thickness with high precision, to specify morphological features and properties of its microstructures. Optical scanning of an optic disk and peripapillary retina gives a chance to estimate up to 20 morphometric parameters [18]. Determination of retinal nerve fiber layer (RNFL) thickness in peripapillary zone reflects a condition of nerve fibers and extent of their defeat. It is shown that in glaucoma there is a thinning of RNFL and a neuroretinal rim [19]. A number of researches testify that RNFL thickness correlates with changes of vision field and with morphometric parameters: Rim Area, Disk Diameter, Cup Diameter, Cup/Disk Area [20]. It has huge value for diagnostics of glaucoma damage extent, monitoring of pathological process, and also efficiency of medicamentous, laser and surgical treatment.

Strahov V.V., Alekseev V.V., Ermakova A.V. consider the nerve parameters characterizing a neuroretinal rim (Horiz. Integrated Rim Width (Area) and Rim area) the most informative in early diagnostics of POAG as they are connected to the optic disk sizes to a lesser extent and correlate with peripapillary nerve fiber thickness (Avg. Thickness) [21]. The maximum importance in monitoring of glaucoma have thickness parameters of perypapillary nerve fibers in upper temporal, lower temporal segments (AUC = 0,7863 RNFL IT and AUC = 0,7827 ST Thikness) and average value of perypapillary nerve fibers thickness (RNFL Average Thikness). In early diagnostics of OCT parameters of retinal ganglion cells complex (GCC) are the most sensitive according to Shevchenko M.V. and et al., they are: AUC = 0,9271 for GCC Average, AUC = 0,9107 for GCC Superior, AUC = 0,8894 for GCC Inferior, AUC = 0,8725 for GLV. And among parameters of an optic disk the most relevant is the volume of neuroretinal rim (Rim Volume, AUC = 0,7602) [22]. Spectralis OCT of an optic nerve head gives a clear understanding of volume and area of neuroretinal rim even in an initial stage of POAG and to a greater extent in stages II, III of the disease [23,24]. In general, OCT in the stage I of POAG allows to reveal existence of pathological changes in 74% of observations. It was found out by Kryachko N.S., Ivanchenko O.V. and et al. that there is a progressing reduction of average thickness of GCC from norm to stage I of glaucoma, and even bigger reduction in stages II and III. Objective measurement of the parameter GLV showed growth from norm to stage I of glaucoma, and further growth in stage II, and bigger increase in stage III [25]. Jarcev A.V., Strahov V.V., Alekseev V.V. and et al. (2013) found reliable structural and functional pathological changes in external layers of retina in POAG, revealed correlations between a condition of structure and function of a pigmentary retinal epithelium, proved the importance of OCT for early detection of POAG [26].

Introduction of OCT in algorithm of dynamic supervision of patients with glaucoma will allow a practicing doctor to optimize treatment tactics. OCT considerably expands diagnostic research possibilities of structural and morphological retinal changes in a macular zone in patients with DR and DME. Retinal thickness is defined from a vitreoretinal surface to an interface, formed by segments of photoreceptors, and in norm varies from 200 to 275 microns, and in fovea is from 170 to 250 microns [12]. Measurement of retinal thickness in macular area is a key point in diagnostics and tactics of treatment.

According to OCT primary thinning of a ganglionar cells layer of the paracentral retina and a nerve fiber layer of a macula in patients with diabetes mellitus type 2 was revealed. It correlated with duration of a disease [8]. These data assume anatomic and functional interrelation between glaucoma and diabetic defeat.

HRT is a method of a confocal scanning laser ophthalmoscopy appeared in the last decade of the 20th century. High sensitivity (more than 80%) and specificity (more than 90%) of this method gave a chance to ophthalmologists to apply it to assess the dynamics of glaucoma, efficiency of surgical and medicamentous treatment [27].

Data obtained by OCT or HRT methods provides an ophthalmologist with detailed information about pathological process, can be used independently and supplement each other a well. There are some technical differences in the principles of optic disk delimitation (OCT — on edge of a layer of a retinal pigment epithelium, HRT on a scleral ring), and also in a method of definition of the plane which divides excavation and neuroretinal rim [28,29].

According to OCT in norm RNFL thickness is 110±7mm, Rim area is 1.37±0.25mm. And according to HRT RNFL thickness is 237±45.8mm, Rim area is 1.68±0.4mm. These parameters authentically decrease in patients with POAG when progressing from the stage I to stage III. Thus, the Cup/Disk Ratio which in norm is 0.4±0.11mm (by results of OCT) and 0.3±0.1mm (according to HRT), authentically increases [30].

However, it was revealed that OCT provides earlier detection of glaucoma optical neuropathy in comparison with HRT [31].

The method of a computer retinotomography can be suggested for calculation of peripapillary chorioretinal atrophy area PPA (β — zone) in patients with glaucoma. The origin of β — zone is connected with an atrophy of a pigmentary epithelium of retina and choriocapillares, and in

norm it is observed in 15-20% of cases. The A-zone characterized by choroidal thinning, is generally noted in healthy people. Existence of PPA β — zone is regarded as prognostically unfavorable marker of a disease along with other risk factors of glaucoma. Kuroedov A.V., Ogorodnikova V.Ju. and coauthors (2009) established authentically significant increase in PPA area in developed and advanced stages of various forms of glaucoma, in relation to PPA area in the initial stage of a disease. The changes of PPA in temporal sector are common for patients with initial POAG, which then move to upper temporal sector (developed stage) and further (advanced stage) equally along all perimeter of optic disk with more expressed defeats in the lower pole [20].

According to Hwang D.J. and et al., RNFL thickness increases in patients with diabetic retinopathy that correlates with degree of diabetic macular edema [32].

The great interest represents investigation of a morphological structure of retina and optic disk in patients with a combined pathology (glaucoma and diabetic retinopathy).

Currently, OCT and HRT became irreplaceable in diagnostics of both glaucoma and DR in view of speed of application, high sensitivity of a method, noninvasivity, safety and informational content. OCT and HRT are the main methods of an assessment of efficiency of therapeutic and surgical treatment.

Since 1985 and at present the principal method of therapy of diabetic retinopathy and prevention of proliferative process is panretinal photocoagulation PRP. The pathogenetic sense consists in extensive laser destruction of retina for the purpose of replacement of coagulated tissue with cicatrical tissue which consumes oxygen in smaller amount. Thus, partial pressure of oxygen in retinal layers increases, retinal oxygenation gets better that leads to the reverse development of neovascularization and exudation [12].

The absolute indication to PRP is proliferative stage of diabetic retinopathy. According to different authors regress of a neovascularization is observed with a frequency from 50 to 85%. It is well-known that PRP leads to narrowing of peripheral vision field, temporary decrease in differential light sensitivity in the central vision field and to short-term violation of color sight. One of the most widespread complications is an occurrence of macular edema leading to a decrease in visual acuity which can gain resistant state. According to recommendations of ETDRS for treatment of diabetic maculopathy ophthalmologists use focal laser photocoagulation of microaneurysms with signs of transudation and retinal vascular abnormalities, a «lattice» technique in diffuse macular edema and their combination [33].

Laser treatment is considered a gold standard against focal DME. According to Balashevich L.I., Gacu M. V application of subthreshold microphotocoagulation for treatment of macular edema is more efficient than suprathreshold laser techniques [34]. Despite promising results, laser photocoagulation was not significantly effective as monotherapy in patients with diffuse and cystoid macular edema. And recently it is considered reasonable to use antiangiogenic therapy with subsequent retinal laser photocoagulation for treatment of DME and DR [35].

In 1948 for the first time Michaelson hypothesized the existence of angiogenesis mediator, the «X-factor» which chemical structure remained not investigated for a long time [36]. In 1989 the Italian scientist N. Ferrara retrieved a molecule of VEGF-A, playing the main role in the cascade of pathological processes in neovascular diseases, from cells of bull hypophysis [37]. And by 1996 during numerous researches the significant role of VEGF-A in intraretinal angiogenesis activation was proved [38]. The same year Bevacizumab molecule (Avastin) was received which has been used actively in oncological treatment since then. Pegaptanib («Macugen») — oligonucleotide, which has ability to connect selectively and possesses high affinity to vascular endothelial growth factor, was synthesized in 2000. In 2004 it became the first officially permitted antiangiogenic medicine for intravitreal injection. But in DME therapy it was less effective [39].

In 2006 Ranibizumab («Lucentis») was implemented for treatment of wet age-related macular degeneration in the world ophthalmologic practice. It represents a Fab-fragment of recombinant humanized monoclonal anti-VEGF-antibody. Since February 2011 in Russia Lucentis was approved and began to be used for treatment of diabetic macular edema [33].

The retrospective analysis of research data Early Treatment Diabetic Retinopathy Study (ETDRS) found that 40% of patients showed improvement of visual acuity in next 3 years after focal laser photocoagulation. And data of Diabetic Retinopathy Clinical Research Network (DRCR.net) speaks about improvement of visual functions after a course of antiangiogenic theraphy to 51%, 47% and 62% after 1, 2 and 3 years respectively [40]. On the basis of the results of randomized multicenter researches (RESTORE, DRCR) a conclusion was made that the method of intravitreal injection of Lucentis either combined with laser photocoagulation or monotherapy is more effective than laser treatment [37,41].

Treatment of neovascular glaucoma (NVG) is a complex problem in view of an inefficiency of conservative therapy and high risk of complications in the operative and postoperative period. Traditional method of neovascular glaucoma treatment in combination with DR is panretinal laser photocoagulation which efficiency is confirmed by the researches DRS 1972-1976, ETDRS 1980-1990 [7]. If after PRP the rubeosis of iris and iridocorneal angle remains or progresses, ophthalmologists apply to antiangiogenic therapy as an additional treatment [12,33]. During a number of researches it was proved that after intravitreal injection of angiogenesis inhibitor full or partial regress of neovascuarization of retina, iris and iridocorneal angle was revealed [42]. The data obtained by Botabekova T.K. and et al.

proved that injection of VEGF inhibitor Lucentis in the anterior chamber in NVG leads to a considerable regression of neovascularization and in combination with surgery allows to reach lasting hypotensive effect without additional medicamentous therapy, excludes occurrence of hemorrhagic complications during surgery and early postoperative period [43]. Thus, Bikbov M. M., White YU.A. and et al. confirm that use of anti-VEGF-drugs in NVG allows to reduce risk of hemorrhagic complications in the subsequent surgical and laser treatment, to reach much higher hypotensive effect in the remote terms [44] and also to prevent an excessive scarring of tissue of a filtration pillow [45].

According to a number of researches, Ranibizumab can provoke transitory lifting of the intraocular pressure (IOP) [46,47]. Good T. J., Kimura A. E. speak about essential and long increase of IOP after intravitreal injections of anti-VEGF-drugs and assume possible risk of further rise of IOP in patients with predisposition to glaucoma [48]. Höhn F., Mirshahi A. assume that short-term rise of IOP after Ranibizumab treatment can depend on surgical technique of injection [49].

Development of algorithm of medicamentous prevention and treatment of IOP jumps after injection deserves special attention. Some authors suppose that there is no need of presurgical prevention [50], and consider reasonable to apply hypotensive therapy in patients after numerous intravitreal injections of anti-VEGF drugs, especially in patients with glaucoma [51].

Despite all the achievements in therapy and diagnostics of both glaucoma and diabetic retinopathy the influence of antiangiogenic treatment on dynamics of clinical and morphological parameters in patients with combined pathology still remains insufficiently investigated. Research of angiogenesis factors, clinical and morphological markers during anti-VEGF therapy will promote deeper understanding of mechanisms of development and progression of glaucoma in patients with diabetes mellitus type 2. It will allow ophthalmologists to develop new approaches to an assessment of diabetic and glaucoma damage extent, prognosis and therapy efficiency.

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