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Role of Vitreous in Pathogenesis of Diabetic Retinopathy

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Abstract

Diabetic retinopathy (DR) is one of the most important medico-social and economic problems of modern healthcare. This review of the literature presents the generally accepted and new views on the development of diabetic retinopathy. At the same time, opinions that contradict the generally accepted views are also presented. Separately collected information about the possible involvement of the vitreous in the development of this complication of diabetes.

Keywords: Diabetic retinopathy; Vitreous; Pathogenesis

Introduction

Diabetic retinopathy (DR) is one of the most important medico-social and economic problems of modern health care. Loss of vision as a result of its development and progression remains a serious problem, despite the improvement of glycemic control methods, the success of lasercoagulation and vitreoretinal surgery [1].

Difficulties in treatment of DR are determined by the lack of a common understanding of the mechanisms of development and pathological processes in the back of the eyeball [1,2]. This may be a result of the one-sided view to the pathophysiology of DR, as a process that develops only in retina and, mainly, due to the influence of systemic factors.

Review

The development and progression of DR is a consequence of a cascade of biochemical and hemodynamic disorders, leading to the gross structural changes in both the retina itself and the tissues bordering it. The processes proceeding with this are determined by genetic predisposition, but their implementation is determined by ontogenesis factors [3]. Despite the fact that the mechanisms underlying these disorders were studied for more than a decade, they are not fully disclosed. As a result, the pathogenesis of DR is still the subject for discussion and research, some of which contradict the already generally accepted positions [4]. The factors that play a significant role in the development and progression of DR are multiple, and they interact closely and potentiate each other. Discoveries of the last decades allow us to consider DR no longer as a process affecting only the vessels of the retina [5]. The involvement of neuronal and glial tissues in the development of the diabetic process in the retina [4], as well as disorders of the choroidal blood circulation [6], were revealed and proved. According to the conventional view, in the basis of the pathogenesis of DR there is a damage to the hematoretinal barrier (HRB) caused by complex biochemical processes, started by the systemic manifestations of diabetes [4].

Hyperglycemia plays a leading role in the initiation and progression of DR. Two major studies, Diabetes Control and Complications Trial (DCCT) in 1993 and United Kingdom Prospective Diabetes Study (UKPDS) in 1998 showed that hyperglycemia is the etiological basis for the development of DR [7]. It induces non-enzymatic glycation of proteins [2,8], oxidative stress [9] and activates protein kinase C [10]. Hyperglycemia also activates the effect of growth factors, cytokines [11], vasoactive factors [12], which cause retinal damage at the cell level and lead to the development of functional changes in the early stages of the disease, and structural disturbances in future. As a result of hyperglycemia, endothelial dysfunction develops [13], followed by the death of endotheliocytes, pericytes, neuronal and glial cells, as well as the proliferation and migration of endothelial cells, etc. [14]. Such microvascular disorders lead to plasma leakage through the damaged vessels, as is the case with nonproliferative DR, and neovascularization of the retina, presumably secondary to ischemia, which occurs during proliferative DR [15]. However, there is an opposite opinion. So, Arden and Sivaprasad demonstrated, in the experiment the high resistance of endothelial cells of retinal capillaries to hyperglycemia in comparison with other retinal cells.

An additional factor that may contribute to the development of endothelial dysfunction on the background of hyperglycemia, considered by authors is an oxidative stress [13,16]. On the background of increasing oxidative stress, damage to glycocalyx endotheliocytes is observed, which is manifested in the predominance of vasoconstrictor effects, increased secretion of adhesion molecules and pro-inflammatory cytokines, reduced NO production, and increased leukocyte adhesion to the surface of retinal endotheliocytes [17].

Leukocyte adhesion, registered at the early stages of the disease, indicates the existence of another pathogenic mechanism of damage to the retina in diabetes mellitus - chronic inflammation of low-intensity. It has been found that increased adhesion of leukocytes to the inner surface of the vascular wall causes the death of endotheliocytes and pericytes, disturbance of HRB, the formation of microaneurysms and acellular capillaries, and their obliteration [18]. The accumulation of adhesion molecules and proinflammatory cytokines in the retina and in the vitreous due to the damage of HRB correlates with the degree and severity of DR [19]. However, Klein et al. revealed that the close correlation between the severity of DR and markers of endothelial dysfunction and inflammation in the systemic circulation, detected in the early stages of the disease, is no longer registered 15 years after the onset of diabetes. This suggests that in the long course of the disease the level of markers of endothelial dysfunction and inflammation in vitreous is not dependent on their systemic level and flow from the bloodstream due to damaged HRB, but is determined by local changes in the affected retina or vitreous. This is also supported by the fact that in patients with proliferative DR and tractional retinal detachment, adhesion molecules level in vitreous is significantly higher comparing to the one of patients with proliferative DR complicated only with vitreous hemorrhage [20].

Another actively studied mechanism for the development of DR is the effect of various growth factors and cytokines [21]. The key point in the development and progression of DR is the increased production of vascular endothelial growth factor (VEGF) in response to ischemia, which initiates the pathological permeability of retinal vessels, activation of endothelial cell migration and proliferation, the development of intraretinal edema and the growth of fibro vascular tissue [22]. Emission of VEGF is caused not only by ischemia and hypoxia, but also by hyperglycemia, inflammatory reactions, oxidative stress, and mechanical tissue damage [22]. The effect of other growth factors and cytokines is again aimed either at suppressing or at increasing the activity of VEGF [23]. It is also known that many retinal cells can produce this cytokine: Cells of the retinal pigment epithelium, pericytes, endothelial cells, Müller cells, astrocytes and hyalocytes [23].

At the same time, the results of some studies suggest that, perhaps, the action of VEGF in the initiation of diabetic retinal damage starts much earlier. According to the observations of a number of researchers, in patients with diabetes without any signs of DR, surprisingly low levels of VEGF in the fluid of the anterior chamber are registered, comparing to the patients without diabetes [10,24]. It is known that the level of VEGF in the anterior chamber fluid correlates with its level in vitreous [25]. Authors themselves do not focus on this fact. However, a decrease in the activity of VEGF, a survival factor for endotheliocytes, pericytes, glial cells and retinal neurons, is not entirely safe and can lead to increased apoptosis of these cellular elements [4]. Enhancing of apoptosis is clinically shown by the appearance of acellular capillaries, their obliteration and formation of ischemic zones [26] and early neurodegeneration in retina [4]. Chad, Reiter et al. consider that the decrease in the activity of VEGF may be caused by the disorder of VEGF receptors activity on the cell surface in response to insulin deficiency or insulin resistance [27]. It is possible that such a mechanism complements damages caused by other mechanisms, and, possibly, resulting from insulin resistance, is manifested even somewhat earlier. A similar assumption about the involvement of VEGF in the development of early stages of age-related macular degeneration was expressed by Witmer et al.

The data of studies of the level of VEGF in the nonproliferative stage of DR are also contradictory. In mice with diabetes, an increase in VEGF in all layers of the retina is recorded even before the development of proliferative DR [28]. However, clinical studies indicate that the level of VEGF remains within the normal range innon-proliferative DR, despite the formation of ischemic foci, microaneurysms and other changes in the retinal vessels [29]. But, given the fact that in the preclinical stage of the disease, the level of VEGF was below normal, as mentioned by Aiello et al., Selim et al. and Kuzmina et al., its normal levels in non-proliferative DR are already relatively elevated and can initiate such clinical manifestations of non-proliferative DR as microaneurysms and intraretinal edema. Only a little later, in response to the formation of ischemic zones and the damaging effect noted above, factors are triggered by an increased expression of VEGF, which is detected only at proliferative DR or diabetic macular edema [30]. According to generally accepted views, an increase in VEGF causes damage to HRB, increased permeability of the vascular wall, enhanced proliferation of endothelial cells by the formation of micro-aneurysm, and at the proliferative stage of DR is the cause of vessels growth [22]. The abovementioned suggests that the expression of VEGF passes through successive phases depending on the stage of the underlying disease: from depression at the preclinical stage of DR to pronounced expression in proliferative DR and diabetic macular edema [31].

At the same time, there are a number of questions that cannot be answered by studying only the processes occurring in the retinal tissue. For example: why are the changes in the retina unique, and there is only thickening of the capillary basement membrane in the cerebral cortex (which is identical to the retina in embryogenesis) in response to metabolic disorders in diabetes? Why does the adhesion of leukocytes occur in certain parts of the capillaries (where microaneurysms are later formed), and not along the entire vessel [32]. Why do microaneurysms grow in the direction of vitreous, and often, starting their growth from a vessel in the inner nuclear layer,

eventually turn out to be found in vitreoretinal space [33]. If the inflammatory process is a damaging mechanism caused by hyperglycemia, why is there no information in the literature about a more severe course of DR in type 1 diabetes with an autoimmune mechanism of development? If the ischemic zones are the source of vascular endothelial growth factor (VEGF), why is its higher content registered in the area of bursa premacularis [34], and not on the periphery of the retina, where ischemic zones are more extensive? Why, despite the blocking of the ischemic zones after pan-retinal laser coagulation, proliferative DR does develop in 10%-30% of observations [35]. As a result, the use of VEGF inhibitors gives only a temporary positive result, while the removal of vitreous promotes a long-lasting therapeutic effect, without accumulation of VEGF in the vitreal cavity in the long-term period [36].

Thus, the pathogenesis of DR is complex and consists of a number of interrelated mechanisms. Existing theories of the development of DR reflect complex changes in the retinal layers, but do not fully explain the developing pathological mechanisms. Probably, the study of processes occurring only in the retina is not enough for a complete understanding of the pathophysiology of DR.

As noted above, the main attention in studying the pathogenesis of DR for a long time has been riveted to changes in the retina, developing as a result of systemic metabolic disorders [37]. Such views on pathogenesis did not contribute to the answer to questions concerning the initiation and development of DR.

The development of vitreous-retinal surgery technology, which started in the 70s of the last century, was largely initiated by the insufficient results of the traditional methods of that time for the treatment of proliferative DR. Despite the fact that the main goal of vitrectomy at that time was mainly to restore the transparency of optical media, the positive results obtained in many patients were maintained for a long time. This was the stimulus for studying the role of vitreous in the pathophysiology of proliferative DR.

If we talk about the role of hyperglycemia, complications of diabetes are characterized by impaired metabolism of glycose-aminoglycans and protein components of the extracellular matrix. Excessive saturation of the extracellular matrix with hyaluronic acid, caused by high glucose concentration, not only disrupts the structural integrity of tissues, but also affects the metabolic response of cells due to a number of effects depending on the molecular weight of hyaluronic acid polymers [38].

There is the cell proliferation and accumulation of matrix in the retina, neovascularization of not only the retina, but also the formation of fibrous vascular membranes between the retina and the vitreous body at proliferative DR. Traction retinal detachment due to the formation of such contractile pre-fibrous membranes is just one of the main causes of blindness in proliferative vitreoretinal diseases and proliferative DR. The formation of these membranes occurs due to the proliferation and migration of cells and the excessive formation and deposition of extracellular matrix proteins and the high activity of angiogenesis in the retina. Fibrovascular membranes are mainly composed of different cell types, such as macrophages/monocytes, hyalocytes, laminocytes, fibroblasts, retinal glial cells, and vascular endothelial cells.

Hyalocytes are the structural component of the vitreous body. They are localized in the vitreous cavity at a distance of about 50 μm from the inner surface of the retina and concentrated in front at the base of the vitreous and behind the optic disc. Hyalocytes belong to the family of monocyte macrophages. They are formed in the bone marrow, mature in the vitreous cavity, actively support the transparency of the vitreous body in physiological conditions. Hyalocytes have a suppressive effect on the proliferation of endothelial cells and cells of the retinal epithelium. Diabetic hyalocytes have a form different from that of a healthy eye, and their number increases in diabetes [39].

Kita T et al. suggested that hyalocytes can be one of the sources of connective tissue growth factor (CTGF) and may play a role in the formation of the fibrotic membrane in proliferative DR [39].

Wang L suggested the possibility of participation of hyalocytes not only in the pathogenesis of proliferative vitreal diseases, but also in immunological disorders [40]. In fact, if we assume that DR is an autoimmune process, then only hyalocytes can take responsibility for changes in the vitreous body- as a source of antibodies in the chain of the autoimmune process.

Machemer et al. during the experiment in the eyes of monkeys with proliferative retinopathy showed that the visible changes in the eye fundus were caused by pigment epithelial cells that could give metaplasia into macrophages or fibrocyte-like cells with active proliferation and the ability to form collagen, forming clusters not only under the detached area of the retina, but also in the vitreous cavity, directly behind the lens. The same cells, when transplanted into the other eye, could be transformed into macrophages or fibrocytes, or be reversed into typical pigment epithelium cells [41].

Other- retinal glial cells- can form areas that grow inward through the inner limiting membrane or outward through the outer limiting membrane and form, respectively, pre- and retroretinal membranes. So, there is no contraction of the vitreous body itself, but traction and contraction of cells and membranes formed by massive proliferation of mainly the pigment epithelium and glial cells. Therefore, massive periretinal proliferation is synonymous with proliferative vitreoretinopathy [41].

Activated T-lymphocytes, B-lymphocytes and macrophages were found in the epiretinal membranes, so it was logical to assume the role of cytokines in the development of DR.

El-Asrar et al. showed an increase in the level of pro-inflammatory cytokines in the vitreous. These cytokines are formed mainly by myofibroblasts and vascular endothelial cells. One of the studied cytokines, the monocyte protein

chemoattractant MCP-1, leads to angiogenesis, firstly, not requiring the presence of inflammatory leukocytes, and secondly, by activity equal to angiogenesis, triggered by vascular endothelial growth factor VEGF [42].

In another work, the same authors showed an increase in MCP-1 monocyte chemoattractant protein, soluble intercellular adhesion molecule-1 (sICAM-1), interleukin 1-betta, and a colony-stimulating factor of granulocyte macrophages (GM-CSF) in a vitreal fluid at proliferative DR, suggesting the role of subclinical chronic inflammation in the vitreous body in the progression of proliferative DR [42].

And with regard to VCAM-1, its elevated level is considered protective without diabetes, and pro-inflammatory in diabetes. And its level may increase not only in hyperglycemic states, but also in hypertriglyceridemia, which does not eliminate the issue of lipotoxicity in the pathogenesis of chronic complications of diabetes [43].

There are a number of works that have studied the content of other proinflammatory cytokines and chemoattractants in the pathogenesis of proliferative DR: this is a factor that stimulates macrophage colonies (M-CSF) and IL-13- these factors stimulate the formation of fibrovascular membranes through the formation of periostin; macrophage-attracting chemokines (CCL2, CCL 3, and CCL4) are involved in the neovascularization process in a mouse model [36]; transforming growth factor-β (TGF-β), whose activity is increased inproliferative DR and proliferative vitreo-retinal diseases. Other functions of this cytokine are regulation of cell growth, differentiation, apoptosis, and the function of immune cells [39].

Connective tissue growth factor (CTGF), also known as CCN2, induces the formation of extracellular matrix, such as collagen and fibronectin, which leads to fibrosis. The expression of this factor is increased in many diseases involving fibrosis, such as scleroderma and liver cirrhosis. Published data confirm that CTGF is induced by TGF-β. It is assumed that CTGF plays a role in the pathogenesis of proliferative DR and proliferative vitreo-retinal diseases- it is formed in large quantities in the membranes of eyes with proliferative DR and proliferative vitreo-retinal diseases, however, the source and stimulator of excessive formation of CTGF remains unclear. Previously, it was believed that retinal pigment epithelial cells are a key element of proliferative vitreo-retinal diseases, but several studies showed that hyalocytes, glial cells, vascular endothelium cells and fibroblast-like cells also play a significant role [39].

The tumor necrosis factor (TNF) -alpha is found in the extracellular matrix, as well as on the luminal and subluminal surface of infiltrating vessels in the membranes in proliferative DR. TNF-alpha is found in high concentrations in the retina, but its concentration in the vitreous body is low. Therefore, Limb et al. suggested the presence of some mechanisms mediating the action of TNF-alpha in the vitreous. The authors concluded that the severity of proliferative DR depends on the amount of soluble receptors for TNF in the vitreous, regardless of the presence or absence of hemorrhages and/or surgical intervention in the fundus. These receptors are supposed to protect cells from TNF-alpha by blocking the activity of this cytokine. However, in proliferative DR, the authors showed elevated levels of TNF-alpha and a decrease in the content of soluble receptors in the vitreous body, which suggested the absence of protective mechanisms to the effects of TNF-alpha in severe proliferative DR [20].

Fibronectins are large glycoproteins found in plasma, in the cell matrix and on the cell surface. They provide intercellular and cell-matrix interactions and thus play a role in the formation and reconstruction of tissues. Different variants of the fibronectin molecule are encoded by one gene, the difference in their primary structure is due to alternative splicing of the primary mRNA transcription. Most fibronectin is produced in the liver. And molecules in the sub-endothelial and connective tissue are formed locally by endothelial cells and fibroblasts. Elevated levels of cellular fibronectin in plasma indicate a loss of polarization of endothelial cells or vascular damage. Kanters S et al. (2001) showed a significant increase in fibronectin levels in patients with diabetes (4.3 ± 2.8 μg/ml) compared to the patients with ischemic stroke (2.0 ± 0.9 μg/ml), reno-vascular hypertension (1.7 ± 1.1 μg/ml) and healthy (1.4 ± 0.6 μg/ml) subjects. The multivariant analysis showed that the high level of triglycerides, current or previous smoking, and an increased level of albumin excretion in the urine were independently associated with elevated levels of circulating cell fibronectin in diabetes. The authors suggest that cell fibronectin may be a marker for the activation of endothelial cells, especially in diabetes [44].

Roy et al. showed increased levels of fibronectin and type IV collagen formed by endothelial cells in diabetes. Moreover, the increase in the level of mRNA fibronectin persisted for several weeks even after normalization of normoglycemia. The authors suggested that hyperglycemia induces further self-sustaining changes in gene expression [45].

Also in recent years, there was shown the role of neurotrophic factors such as neuregulin 1 (NRG1), nerve growth factor receptor (NGFR) and growth factor isolated from platelets (PDGF) in the formation of fibrovascular membranes in proliferative DR [46].

Thus, the pathogenesis of proliferative DR is a complex, multifactorial process involving not only the systemic manifestations of diabetes: hyperglycemia, dyslipidemia, but also the mechanisms of chronic inflammation induced and maintained by factors whose number increases as the pathogenesis of this complication of diabetes is studied. Today, albeit scattered, the facts about the role of the vitreous body in this process give us reason to consider it a rather important object for further research. Moreover, if the role of vitreous in the development of advanced stages of the proliferative DR is obvious, it requires a deeper study at the early stages of non-proliferative DR.

Limitations of Presented Review

In our work, little attention is paid to the role of oxidative stress in the development of changes in the vitreous body, to

changes in oxygen circulation through retina with the development of posterior vitreous detachment. In general, this paper covers only the biochemical component of vitreous changes in diabetes mellitus. Perhaps in a subsequent publication we will highlight issues related to the biomechanical changes associated with biochemical restructuring of the vitreous body. Namely, the role of traction effects of the vitreous body in the development and progression of diabetic retinopathy.

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