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# The role of inflammation in diabetic retinopathy in patients with type II diabetes; potential therapeutic perspectives

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ABSTRACT

Diabetic retinopathy is one of the major causes of visual impairment and blindness in adult population. The pathology is complex, the metabolic changes induced by the hyperglycemic environment leading to neurodegeneration, microvascular damage, with secondary ischemic and inflammatory changes in the retina. This review aims to update the literature data related to the role of inflammation in the onset and progression of diabetic retinopathy. Thus, the molecular and biochemical mechanisms triggered by excess glucose increase the expression of genes involved in inflammatory processes, which leads to the synthesis of inflammatory cytokines such as Il1, Il6, TNF alpha as well as complement activation. Furthermore, recent evidence has demonstrated that both systemic and ocular prolonged inflammation are correlated with the progression of diabetic retinopathy. In conclusion, preventing and/or reducing the progression of diabetic retinopathy requires both rigorous glycemic control in diabetic patients and targeted interference of the specific inflammatory pathways involved.

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## Introduction

Among the ocular complications affecting patients with diabetes mellitus, diabetic retinopathy (DR) has the highest prevalence, affecting approximately one-third of diabetic patients [1]. Of these, around 3.9 million individuals across all age groups experience moderate and severe visual impairments or complete vision loss due to diabetic retinopathy [2]. Despite the significant milestone achieved with the discovery of the intravitreal anti-VEGF agents, diabetic retinopathy is the leading cause of vision loss among the working-age population [3,4]. Consequently, the financial impact on society is very high, warranting the monitoring and early treatment of diabetic retinopathy.

The condition presents a complex physiopathological mechanism, with neuro-vascular, inflammatory and degenerative changes being described, which usually preceded the microangiopathic changes that are detectable by clinical examination [5-7]. Recent evidence shows that chronic hyperglycemia induces neurodegenerative changes in the retina. Muller cells disfunction causes an imbalance in the retinal expression of growth factors and cytokines, leading to neural apoptosis and glial activation. Early loss of pericyte, increased vascular permeability, and segmentary vascular occlusions lead to microvascular damage, with intraretinal dot and spot hemorrhages, extravasation of fluid and lipoproteins in the retinal layer, and focal ischemia.

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Recent studies evidenced the key role of inflammation in the pathology of type 2 diabetes, the correlations being bi-dimensional. On the one hand, metabolic dysfunction and accumulation of toxic metabolites are triggers for the activation of inflammasomes and the release of proinflammatory cytokines in response to damage-associated molecular patterns (DAMPs) [8,9]. On the other hand, several clinical and experimental researches revealed novel insights into the effect of both systemic and ocular prolonged inflammation in the progression of diabetic retinopathy.

The present review aims to present the latest data from the literature regarding the role of inflammation in the onset and progression of diabetic retinopathy, as well as to explore potential therapeutic implications.

## Discussions

*Molecular and biochemical mechanisms of retinal cell damage induced by hyperglycemia*

At the cellular level, hyperglycemia induces the accumulation of the glycolysis intermediate product, dihydroxyacetone phosphate (DHAP), whose reduction reaction generates the formation of glycerol-3-phosphate, directly involved in de novo synthesis of diacylglycerol (DAG), with secondary activation of protein kinase C (PKC) [10].

Additionally, hyperglycemia has the effect of saturating the normal glycolytic pathway (hexokinase pathway) [11]. The excess glucose will be metabolized through alternative pathways, leading to direct or indirect cellular damages, increased highly reactive oxygen species, activation of cytokines, and accumulation of toxic metabolites [11,12].

The pentose phosphate pathway (PPP) produces Ribulose 5-phosphate (Ru5P), which is essential for nucleic acid synthesis, as well as $CO_2$, a reaction facilitated by the reduction of 2 molecules of NADP+ to NADPH (reduced nicotinamide adenine dinucleotide phosphate). NADPH plays a crucial role in anabolic processes, such as nucleic acid and lipid synthesis, as well as in the reduction of oxidized glutathione (GSSH), thereby maintaining an elevated level of glutathione (GSH) necessary for reducing oxidative stress. However, in macrophages and neutrophils, NADPH also has a pro-oxidative effect, as it can generate ROS through the enzyme NOX2 (NADPH oxidase 2). The protective role of NADPH is diminished in diabetes due to its dependence on G6PD activity, which is limited by hyperglycemia. Nonetheless, in endothelial cells, there is an overexpression of G6PD, explaining the relationship between lesion occurrence and disease duration, requiring prolonged elevated glucose levels [13,14].

The polyol pathway involves the metabolism of excess glucose by reducing it to sorbitol under the action of aldoreductase, and it involves the oxidation of NADPH to NADP+. This reaction can increase oxidative stress due to NADPH consumption, and elevated sorbitol concentrations can induce damage by increasing intracellular osmolarity. Additionally, fructose obtained from the oxidation of sorbitol serves as a substrate for the formation of advanced glycation end products (AGEs) [15].

The hexosamine pathway generates UDP-GlcNAc, a step mediated by the enzyme glutamine fructose-6-phosphate amidotransferase (GFAT) [16]. UDP-GlcNAc serves as a substrate for glycosylating serine and threonine residues on intracellular proteins (O-GlcNAcylation), including various transcription factors and signaling proteins. Furthermore, hyper-O-GlcNAcylation activates NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells) [16,17].

The formation of advanced glycation end products (AGEs) is another mechanism contributing to oxidative stress at the level of endothelial cells. Hyperglycemia leads to the non-enzymatic glycation of lipids and proteins, a process known as the Maillard reaction. Examples of endogenous AGEs include glucosepane, pentosidine, and Nε-(carboxymethyl) lysine (CML). The accumulation of AGEs increases the stiffness of vascular walls (through irreversible cross-linking of extracellular matrix collagen) and disrupts the functional integrity of endothelial cells by intracellular accumulation, thus elevating vascular permeability. Additionally, their coupling with the specific receptor (RAGE) ultimately leads to NF-kB activation [18,19].

The activation of PKC and NF-kB increases the expression of genes involved in inflammatory processes, such as COX2 (cyclooxygenase 2), thereby elevating the levels of PGE2 (prostaglandin E2) and Thromboxane A2 [20-22]. Moreover, NF-kB activation enhances the expression of cytokine genes, like IL-6, which play a role in recruiting circulating leukocytes. The overexpression of intercellular adhesion molecules (ICAM1 - intercellular adhesion molecule 1 and VCAM1 - vascular cell adhesion molecule 1) is induced by NF-kB activation, facilitating the adhesion of recruited leukocytes to endothelial cells [20,23]. Circulating interleukin-6 stimulates the production of CRP (C-reactive protein) by hepatocytes. CRP is involved in complement activation and plays a significant role in the clearance of apoptotic cells [24,25]. NF-kB also increases the expression of pro-apoptotic genes, such as Caspase-3. Pro-inflammatory cytokines IL-6 and IL-1 also stimulate the production of the C3 fraction of complement. Complement cascade activation occurs in the choroidal capillaries, where increased levels of C3d, C5b-9, and deposits of membrane attack complex (MAC) have been identified [20,26].

Other effects of NF-kB activation include increased fibronectin synthesis, contributing to the thickening of the basement membrane an imbalance of local vasoconstrictors and vasodilators, with increased

production of ET-1 (endothelin 1), and reduced eNOS (endothelial nitric oxide synthase), leading to capillary luminal constriction [17,26]. Increased expression of TNFα promotes local inflammation, with destruction of intra and extracellular matrix.

Recent studies found that matrix metalloproteinases MMP2 and MMP9 may facilitate the apoptosis of retinal capillary cells, in early stages, possibly via damaging the mitochondria, while later, in the proliferative stage, they help in neovascularization [27,28]. Metalloproteinases are highly sensitive to the accumulation of ROS products and inflammation. The levels of several cytokines, such as Il-1beta and TNF-alfa, are increased in the vitreous samples of patients with diabetic retinopathy and they are correlated with higher activity of MMP2 and MMP9 [28,29]. Moreover, activated metalloproteinases increase the tissue availability of VEGF, by disrupting the hematoretinal barrier, favoring angiogenesis, inflammation, and exudation.

Recent studies found an imbalance between NGF (nerve growth factor) and its precursor pro-NGF in the diabetic retina, which might be related to decreased activity of MMP-7, which is responsible for its cleavage. Reduction of NGF (nerve growth factor), a key mediator for the health of retinal ganglion cells [30], leads to neurodegenerative lesions [12,20,31-34].

These intracellular processes will lead to modifications in the retinal microcirculation, causing endothelial lesions with thickening of the basement membrane and a reduction in the number of pericytes. These changes will result in the dilation of capillary lumens, with the formation of microaneurysms, increased capillary permeability, and diffusion of intraretinal lipoproteins, clinically presenting as edema and hard exudates, capillary obstruction, resulting in the formation of hemorrhages and ischemic zones, and prolonged ischemia contributing to the development of neovascularization [35,36].

*The role of inflammation in diabetic retinopathy*

Inflammation is a non-specific response to injury caused by external pathogens (PAMP), but also to endogenous damaged structures (DAMP). Diabetic retina is associated with chronic low-grade inflammation. Several studies revealed increased levels of various cytokines in vitreous and serum samples of diabetic patients. These changes are triggered by the DAMP pathway, via NLRP3 inflammasome [9]. Inflammation may impact negatively retinal microcirculation by multiple mechanisms. Chronic low-grade inflammation can contribute to endothelial dysfunction in the retinal vasculature [36,37]. Endothelial dysfunction is characterized by reduced nitric oxide (NO) bioavailability, increased expression of adhesion molecules, and impaired regulation of vascular tone. These changes can lead to the breakdown of the blood-retinal barrier, increased vascular permeability, and the development of macular edema, which is a major cause of vision loss in DR [38,39].

Leukocyte adhesion and infiltration in the retinal endothelium and subsequent infiltration into the retinal tissue and release of pro-inflammatory cytokines and chemokines lead to microvascular occlusion, retinal ischemia, the upregulation of vascular endothelial growth factor (VEGF), which can exacerbate endothelial dysfunction, disruption of hematoretinal barrier and retinal neovascularization in DR [40].

Inflammation leads to an imbalance of the fluid-coagulant state, with platelet activation and aggregation, fibrinogen deposits, and gliosis [41]. Microthrombosis can exacerbate retinal ischemia and hypoxia, leading to the upregulation of VEGF and the promotion of neo-vascularization in proliferative DR [36,42].

*Systemic inflammation and DR*

Recent studies have shown a certain degree of correlation between diabetic retinopathy and plasma levels of various inflammatory molecules, including PGE2 [2], IL-6 [43], TNFα, VCAM1 [44], ICAM1, VEGF [45], CRP [46], complement C3 fraction [47], and ET-1 [48].

Numerous researches evidenced that prolonged systemic inflammation is a risk factor for diabetic retinopathy progression. Lipopolysaccharides (LPS), a constitutive element of the outer membrane of gram-negative bacteria [49] were correlated with the onset and progression of diabetic retinopathy, in both experimental and human research [50-53]. In advanced stages of DR, serum LPS were higher compared to controls, probably due to a leaky gut and associated dysbiosis. An experimental study by Vagaja et al [50], on Ins2Akita mice found that chronic repetitive systemic challenge with lipopolysaccharide LPS leads to injury of the capillary endothelium and in vivo thinning of the retina in hyperglycemic mice, but not in healthy controls. Moreover, other experimental studies found that systemic LPS induces activation of microglia via Endothelial Toll-like receptor 4, leading to altered density and morphology of retinal microglia [51-53].

DR and diabetic foot ulcer are both disabling complications of diabetes, which often coexist. Moreover, several studies found a bidirectional correlation, with long-standing non-healing ulcers, as well as superinfected lesions, being risk factors for proliferative diabetic retinopathy [42,54].

In a large study on 6164 patients, an association of psoriasis with diabetes was found to be a risk factor for microvascular complications, including diabetic retinopathy [55]. Recently, during the COVID-19 pandemic, several authors reported rapid progression of DR after severe COVID-19 pneumonia requiring oxygen supplementation, explained by prolonged hypoxia and inflammation [56-58].

*Ocular inflammation and the progression of DR*

There is strong evidence that prolonged ocular inflammation induces higher expression of cytokines and VEGF, thus altering the retinal-blood barrier and promoting leakage, retinal edema, and neovascularization in diabetic patients.

Prolonged cataract healing, especially associated with intraoperative complications was found to increase post-operative risks for NPDR, while the significant influence persisted 5 years after surgery [59-61]. A large study by Chu et al [61] found an increased incidence of diabetic macular edema (DME) in diabetic patients who underwent cataract surgery.

Furthermore, several studies showed that chronic ocular inflammatory disorders, such as uveitis and keratitis, are associated with DR progression [61-63]. Other case reports found that after unilateral posterior uveitis, diabetic patients developed more quickly proliferative DR, compared to fellow eye [61,62].

*Future therapeutic targets*

Recent therapies studied in diabetic retinopathy aim to inhibit the polyol pathway (pterostilbene), block the hexosamine pathway (azaserine, benfotiamine, rhein), reduce AGEs formation, neutralize ROS, suppress NF-kB activation (curcumin, quercetin, resveratrol, green tea extract), block COX2, and target other molecules such as PKC (ruboxistaurin), IL-6 (tocilizumab), IL-1β (tetracyclines), TNFα, and VEGF [6,20,64-66]. Several studies explored the role of anti-inflammatory phytochemicals in diabetic retinopathy, with encouraging results in experimental settings. Administration of Curcumolide, extracted from Curcuma wenyujin, in rats with streptozocin-induced diabetes, resulted in decreased expression of ICAM-1, leukocyte counts, and ultimately attenuated retinal vascular leakage [67,68]. Intraperitoneal injection of andrographolide in mice significantly reduced the retinal expression of early growth response factor 1 (Egr1), with consecutively decrease in the production of inflammatory cytokines IL-1β, IL-6, and TNF-α, and noticeable improvement of diabetic retinopathy [69].

Several experimental animal studies found that long term oral administration of resveratrol in doses of 5 mg/kgc/day alleviate inflammatory changes induced by oxidative stress, by decreasing NF-κB activity and apoptosis rate [70-72]. Moreover, four months administration of resveratrol to diabetic rats improved the elevated levels of plasma TNFα and IL-6 as well as NF-κB activity of polymorphonuclear cells [70]. Soufi et al. [71] found that chronic administration of resvetratrol could be of potential therapeutic use in diabetic retinopathy, by preventing disarrangement and reduction in thickness of retinal layers. Jiang et al. [72] found that resveratrol was able to reverse high-glucose-induced inflammation "metabolic memory" of human retinal vascular endothelial cells by activation of the SIRT1/AMPK/NF-κB pathway. A clinical study of Chatziralli et al. [73] showed that oral supplements with resveratrol were useful in combination with intravitreal anti-VEGF therapy in reduction of diabetic macular edema.

An experimental study on rats with streptozocin-induced diabetes found that vitreous NGF levels increase in early stages which may be explained by an endogenous response for protecting RGCs from degeneration. This adaptative mechanism seems to be impaired after 11 weeks, with retinal neurodegeneration. However, administrating NGF eyedrops improved retinal cell function, being a potential therapeutic target in diabetic retinopathy, as well as in other retinal degenerative diseases [74].

## Conclusions

Together with the diet and lifestyle changes in the contemporary world, the incidence of diabetes and its complications are expected to rise in the next years. The identification of biochemical modifications occurring at the cellular level in diabetic retinopathy plays a significant role in the management of this condition. It enables the potential discovery of biomarkers and the identification of therapeutic targets.

## Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. Informed consent was obtained from all subjects involved in the study.

## Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

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