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Association of serum inflammatory markers and diabetic retinopathy: a review of literature

N.S. GOULIOPOULOS[1], C. KALOGEROPOULOS[2], A. LAVARIS[1], A. ROUVAS[3], I. ASPROUDIS[2], A. GARMPI[4], C. DAMASKOS[5], N. GARMPIS[5], A. KOSTAKIS[6], M.M. MOSCHOS[1]

[1]1st Department of Ophthalmology, University of Athens Medical School, 'G. Genimmatas' General Hospital Athens, Holargos Athens, Greece
[2]Department of Ophthalmology, University Ioannina, Ioannina, Greece
[3]2nd Department of Ophthalmology, University of Athens Medical School, 'Attikon Hospital', Athens, Greece
[4]Internal Medicine Department, Laiko General Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece
[5]Second Department of Propedeutic Surgery, Laiko General Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece
[6]Biomedical Research Foundation (IIBEA), Academy of Athens, Athens, Greece

Abstract. – OBJECTIVE: Diabetic retinopathy is the leading cause of irreversible blindness in the western world, among the working-age people. Its exact pathogenesis, however, remains obscure. Systemic inflammation is regarded to play a significant role in diabetes by contributing, among others, to the development of diabetic retinopathy. This review focuses on the possible involvement of the systemic inflammatory markers in the pathogenesis of diabetic retinopathy.

MATERIALS AND METHODS: We performed a systematic search of the literature of published papers until August 2017 using the PubMed search engine.

RESULTS: We demonstrated that many systemic inflammatory markers contribute to the pathogenesis and progression of retinopathy, while we highlighted in several occasions their usefulness as a key tool in the monitoring of the disease progression and the treatment efficacy.

CONCLUSIONS: To the best of our knowledge this is the first review in the literature that elaborates the possible association of serum inflammatory markers and diabetic retinopathy, a disease that may cause irreversible loss of vision.

Key Words:
Diabetic retinopathy, Inflammation, Serum inflammatory markers.

Introduction

Diabetes Mellitus and Diabetic Retinopathy

Diabetes mellitus (DM) is characterized by hyperglycemia because of the total or relative lack of insulin (Type-1 and Type-2, respectively). Its incidence is reaching epidemic scales and according to the World Health Organization it is expected that there will be 366 million diabetic patients in 2030, twice the number of patients in 2000[1]. Diabetic complications are very common and major causes of morbidity and mortality, including cardiovascular disease, nephropathy, retinopathy, neuropathy, diabetic foot syndrome, and periodontitis[2,3].

Diabetic retinopathy (DR), a diabetic microvascular complication, is present in 35.4% of the diabetic patients[4]. DR is regarded as the leading cause of irreversible blindness among the working-age people in the western world[5,6], and the fifth most common cause worldwide of both preventable vision loss and moderate to severe vision impairment[7].

Epidemiology of Diabetic Retinopathy

DR prevalence is reported to be 77.3% in Type-1 DM (T1DM), and 32.4% in Type-2 DM (T2DM)[7]. According to the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR),

Corresponding Author: Nikolaos S. Gouliopoulos, MD, Ph.D; e-mail: ngouliopoulos@yahoo.gr

DR incidence in T1DM patients was 59% at 4 years, reaching 97% at 25 years[8]. In T2DM patients, its 4-years incidence is reported to be 26%-34% rising to 66% and 72.3% at 10 and 14 years, respectively[9-11].

Classification of Diabetic Retinopathy

Many classification systems are used for DR[12-14]. The International Clinical Disease Severity Scale is based upon the findings of WESDR and Early Treatment Diabetic Retinopathy Study (ETDRS) and consists of 5 stages, 3 of relatively low and 2 of high risk[15]. The first one is "no apparent retinopathy" and no fundus changes are present. The second one is called "mild non-proliferative retinopathy" and only a few microaneurysms exist. "Moderate non-proliferative retinopathy" is the third stage, in which microaneurysms, intraretinal hemorrhages or venous beading are present. The fourth stage is called "severe non-proliferative diabetic retinopathy" and its diagnosis is based upon the ETDRS "4:2:1 rule"[16]. Eyes classified in this stage have severe hemorrhages in 4 quadrants, or venous beading in 2, or intraretinal microvascular abnormalities in 1. Eyes with less severe findings, but more than "microaneurysms only", are classified in the third stage. The fifth stage is "proliferative diabetic retinopathy" (PDR). Neovascularization of the disc, or of the retina, or of the angle, or vitreous hemorrhage, or tractional retinal detachment, identify this stage. As for the diabetic macular edema (DME), it is identified as present or absent, while it is classified as mild, moderate, and severe depending on the distance of the exudates and thickening from the center of the fovea[15].

Risk factors for Diabetic Retinopathy

The risk factors (RFs) for DR are divided into two categories: modifiable and non-modifiable. The most significant modifiable RFs include hyperglycemia, hypertension, hyperlipidemia, and obesity[17]. Further modifiable RFs are sleep apnea[18], prolactin, adiponectin and homocysteine levels[19-21], nonalcoholic fatty liver disease[22], as well as genetic factors, including mutations in the erythropoietin gene promoter[23]. As for the non-modifiable RFs, the most important are DM duration and age of onset, puberty, and pregnancy[17].

Hyperglycemia, expressed by HbA1c values, is the strongest RF for DR development and progression[24]. UK Prospective Diabetes Study (UKPDS) and Diabetes Control and Complications Trial (DCCT) proved that the risk of DR is low when HbA1c levels are $\leq 7\%$[17], while it has been suggested that the risk of DR also reduces by 40% for every 1% decrease in HbA1c values[25].

Hypertension is another major RF[17]. According to UKPDS, in T2DM patients the risk of early DR and DME increases by 10% and 15% respectively, for every 10mmHg increase in blood pressure[26]. However, recent studies question the significance of blood pressure control in DR prevention[27].

As for dyslipidemia, DCCT proved that in T1DM, DR severity is correlated positively with increased triglycerides and negatively with HDL levels[28], while the Hoorn Study found positive associations of elevated LDL levels with hard retinal exudates[29].

Many studies highlight the crucial role of obesity in DR[29,30] claiming that Body Mass Index (BMI) over 31 kg/m^2 in men and over 32 kg/m^2 in women increases the risk of developing DR dramatically[30,31].

Pregnancy in T1DM patients contributes to rapid DR progression, even to vision-threatening stages[32]. As for puberty, WESDR proposed that the patients who are diagnosed with T1DM before puberty develop much earlier DR[33].

Inflammation and DR

The aforementioned RFs explain only partially the etiology of DR. DM duration, HbA1c levels, hypertension, hyperlipidemia, and the age of DM onset together accounted for only 44,6% and 19,5% of total variances of DR and DME, respectively[34]. Therefore many researches investigated other modifiable RFs that could contribute to the disease pathogenesis.

Inflammation has been hypothesized as a potent RF. It is well known that inflammatory activity is elevated in T1DM patients and associated with macrovascular complications[35,36]. Low-grade systemic inflammation is a key mechanism in T2DM pathogenesis, since elevated serum levels of inflammatory markers are observed in healthy people who later develop T2DM, underlying the crucial role of the inflammatory activity which occurs early, even at the stages of insulin resistance and impaired glucose tolerance[37-40].

Lots of studies have evaluated the hypothesis that systemic inflammation is related with DR, by studying the role of several circulating inflammatory markers. With this review, we aim to investigate the role of each serum inflammatory marker

in DR development and progression, to contribute to further understanding of DR pathophysiology, and therefore designate potential therapeutic targets for DR prevention.

Inflammatory Markers

C-reactive Protein

C-reactive protein (CRP) is mainly produced by the liver and also by atherosclerotic plaques, smooth vascular cells, peripheral leukocytes, adipose tissue, and intracardial tissues[41-43]. Acute and chronic inflammatory conditions promote the release of IL-6 and other cytokines, which in turn stimulate the hepatic CRP synthesis[44]. CRP is an acute phase and a non-specific inflammatory biomarker, playing a significant role in the innate immunity, the activation of the classical complement pathway, the enhancement of leukocyte reactivity and the production of cytokines[40,45].

CRP is elevated in several systematic inflammatory conditions, including infections, cancer, rheumatic disease, endothelial dysfunction, obesity and autoimmune diseases[45]. As an inflammatory marker its predictive value is low, whereas its main usefulness is for inflammation screening. High-sensitivity assay for CRP (hs-CRP) detects low (even ≤ 0.3 mg/L) and persistent CRP levels, being thus a significant biomarker of subclinical and chronic inflammation[46,47].

CRP is strongly associated with insulin resistance, central obesity, smoking and greater risk for cardiovascular disease[43,45]. Its levels rise in diabetic patients[34,48], especially in those with worse glycemic control[49], being regarded as a significant RF for diabetes development[38,39,50-54].

The possible associations of CRP with DR have been studied on a large scale with inconsistent results. Many studies found that DR presence is accompanied by significantly elevated serum CRP and hsCRP levels in both DM types[40,55-57], especially in older patients with longer disease duration, suggesting that CRP ≥ 3 mg/L could be identified as an independent RF for DR development[58]. A positive and significant association, which is more pronounced in obese diabetic individuals (BM I > 30 kg/m^2), has been found between CRP and DR[59], proposing that there is a modifying effect of obesity on this association, which could be partially explained by the fact that hepatic CRP production is stimulated by adipocytes[60]. CRP is implicated in DME development as well, indicating that inflammation plays a role in its pathogenesis[61]. Furthermore, DR progression has been observed during pregnancy in diabetic women with elevated CRP levels and worse glycemic control (HbA1c > 6.9%) at the first trimester[46].

On the contrary, several works dispute its role as a pathogenic factor for DR development and progression and its usefulness as a therapeutic or monitoring target, proposing that the association between CRP and DR is not yet established[21,62-66]. Moreover, it has been indicated that within DR patients, CRP levels do not differ according to the disease severity[64,67-69]. Surprisingly, it has also been suggested that elevated CRP levels have a protective effect against DR[70], a finding that was replicated by Blum et al[69], who demonstrated that PDR is accompanied by lower CRP levels. Further studies found a trend for DR progression in patients with higher CRP levels; however this association was not independent and significant[62,66]. Moreover, EUCLID and other prospective studies did not identify a significant association between CRP and DR occurrence, indicating a weak involvement in DR pathogenesis[31,66,71].

Tumor Necrosis Factor Alpha

Tumor necrosis factor alpha (TNF-α) is a pleiotropic cytokine, mainly produced by activated macrophages and T-lymphocytes and also by several cell types, such as mast cells, B-lymphocytes, Natural Killer cells, neutrophils, endothelial cells and smooth muscle cells[72,73]. TNF-α has significant pro-inflammatory properties, being involved in innate and adaptive immunity, cell proliferation, apoptotic cell death, cachexia, inhibition of tumor genesis, stimulation of acute phase inflammation and atherosclerosis development[73-75].

TNF-α serum levels rise in acute and chronic inflammatory conditions, including trauma, rheumatoid arthritis, sepsis, and infection, correlating with their severity, while anti-TNF-α agents are used in the treatment of chronic inflammatory diseases, such as rheumatoid arthritis[72,73].

It is suggested that TNF-α is implicated in DM pathogenesis, by raising the expression of islet amyloid polypeptide in pancreatic β-cells resulting in their death[76], and by contributing to insulin resistance, while in animal models TNF-α is associated with severely impaired glucose tolerance and insulin sensitivity[77].

TNF-α binds to two receptors, TNFR-I (expressed in most tissues) and TNFR-II (expressed in immune system cells)[73]. The binding launches a signaling pathway, activating either the apoptotic pathway or the nuclear factor-kB (NF-kB)[72,78].

Although TNF-α receptors are well established TNF-α antagonists, they can also be regarded as a reservoir of circulating TNF-α, and their soluble forms (sTNFR-I and sTNFR-II) play a crucial role in the regulation of TNF-α signaling[79].

The possible role of circulating TNF-α in DR development and progression has been thoroughly investigated. A positive and significant association exists between DR prevalence (even in early stages) and serum TNF-α levels in both DM types[48,71,80,81], although a few studies rejected this association[82]. According to EURODIAB Prospective Complications Study[80], circulating TNF-α strongly and positively correlates with DR severity, a finding that has been repeatedly confirmed[67,71,81,83]. More specifically, TNF-α has been identified as a strong and independent RF for both PDR and DME[61,67,71,83]. Animal studies demonstrated that circulating TNF-α contributes to increased permeability of retinal endothelial cells[84] and breakdown of blood-retinal barrier[85], giving thus a plausible explanation for its connection with DME. Interestingly, a rise of TNF-α serum levels by 10 pg/mL has been associated with 2-fold increased risk of PDR and/or DME[83]. Furthermore, a prospective study by Roy et al[71] indicated that TNF-α could predict PDR and DME incidence, which elevates up to three times for baseline TNF-α levels ≥3.4 pg/mL.

It has been suggested that serum levels of soluble receptors of TNF-α could also play a role in DR pathogenesis, since their vitreous levels are associated with DR and their involvement in endothelial activation is well established[78,86]. In a population of T1DM patients, DR prevalence was accompanied by increased serum levels of both sTNFR-I and sTNFR-II, and this association was stronger for sTNFR-I[78]. However, according to DCCT study, their prognostic value is limited since they did not correlate with DR endpoints, which include DR progression and occurrence of PDR and/or DME[86].

Interleukin-6

Interleukin-6 (IL-6) is a pleiotropic cytokine, mainly produced by activated leukocytes, monocytes, adipocytes, endothelial cells, islet β-cells, microglial cells, astrocytes, and smooth muscle cells[87,88]. IL-6 is both an acute phase inflammatory marker, regulating the production of acute phase proteins[89] and a marker of chronic inflammation, being involved in the transition from acute to chronic inflammatory status by contributing to the change of leukocyte infiltrate from polymorphonuclear neutrophils to monocyte/macrophages and their recruitment to the inflammatory area[90]. It has an anti-inflammatory function in the acute phase of inflammation[91] whereas in chronic inflammation it exhibits a pro-inflammatory profile[92,93].

IL-6 contributes to T1DM pathogenesis, by getting involved in β-cell destruction. IL-6 affects glucose levels, is associated with obesity and insulin resistance and therefore is directly and indirectly involved in T2DM pathogenesis[94]. Furthermore, IL-6 promotes the development of diabetic complications, either directly or by arbitrating the effects of established RFs, such as blood pressure, glucose levels, and advanced glycation end products (AGEs)[95,96].

Vitreous levels of IL-6 not only contribute to DR development[21], but also correlate with more severe disease stages, especially with PDR and DME[46,97].

Systematic IL-6 levels have been associated with the presence of early and advanced DR stages, and with the disease severity in both DM types[67,80,81]. These findings could be attributed to its contribution in endothelial impairment and leukocyte adherence to retinal endothelium[80], as well as to its synergy with other inflammatory factors, such as TNF-α, IL-1β[67], and progranulin[81]. Furthermore, recently it was proposed that elevated IL-6 plasma levels could detect diabetic individuals with impaired best corrected visual acuity (BCVA), and more precisely levels ≥1.85 pg/mL have 78% sensitivity and 65% specificity for the diagnosis of severely impaired BCVA[98].

On the other hand, according to Multi-Ethnic Study of Atherosclerosis no association exists between IL-6 serum levels and DR prevalence in T1DM[21], suggesting that IL-6 has limited prognostic value for identifying diabetic subjects at high risk for developing retinopathy. Further studies also rejected the presence of a positive and significant association between serum IL-6 and DR prevalence, severity, and progression in both DM types[68,71,82,83,99,100]. Moreover, Loukovaara et al[46] did not identify a role for IL-6 in DR progression during pregnancy and postpartum, a finding that is partially attributed to the participants' coexisting good glycemic control and shorter disease duration.

Intercellular Adhesion Molecule-1

Intercellular adhesion molecule-1 (ICAM-1), one of the cell adhesion molecules (CAMs), is produced by macrophages and endothelial cells

under the regulation of inflammatory cytokines, such as IL-1, TNF-α, and interferon-γ[101]. High ICAM-1 plasma levels are detected in inflammatory conditions[102], and have been associated with the development of hypertension and macroangiopathy[39,102-105].

ICAM-1 mediates the leukocyte adhesion to the retinal vasculature, which in turn contributes to vascular permeability, endothelial impairment and non-perfusion of the capillaries[106,107] playing a key role in the early stages of DR pathogenesis.

Inconsistent findings, regarding the association of circulating ICAM-1 levels and DR, resulted from the performed studies. Many of them did not detect significant differences in ICAM-1 plasma levels between DR and non-DR patients, rejecting its contribution to DR pathogenesis or progression[56,59,67,100,108-113].

On the other hand, significant associations of ICAM-1 plasma levels with DR presence have been found, even in the early disease stages, indicating that systemic inflammation and endothelial dysfunction are also involved in minimal disorders of the retinal vasculature[57,78,114]. DR severity has also been positively correlated with ICAM-1[115]. Moreover, according to the DCCT Study, a selective association exists between ICAM-1 and the development of retinal hard exudates[116]. Furthermore, DME occurrence has been associated with baseline ICAM-1 plasma levels[71,116], and more specifically, the risk for DME rise up to three times for ICAM-1 levels ≥ 165 pg/mL[71].

In conclusion, although the observed significant associations highlight the importance of ICAM-1 in DR pathogenesis, its actual role is still questioned.

Vascular Cell Adhesion Molecule-1

Vascular Cell Adhesion Molecule-1 (VCAM-1) belongs to the immunoglobulin superfamily of CAMs, mediating the adhesion of lymphocytes, monocytes, eosinophils, and basophils to the vascular endothelium and their subsequent recruitment[117]. VCAM-1 is mainly expressed on endothelial cells[118], under the regulation of TNF-α, IL-1β[119], and CRP[120]. VCAM-1, a marker of inflammation and endothelial dysfunction[57], is an essential factor in the pathogenesis of inflammatory diseases, such as arthritis[121].

VCAM-1 promotes the adherence of leukocytes to retinal vasculature, one of the earliest changes in DR pathogenesis[122,123]. Possible associations between VCAM-1 plasma levels and DR have been thoroughly investigated with controversial results. It has been demonstrated that significant associations are present in both early DR stages[57] and PDR[124,125]. Interestingly, Adamiec-Mroczek et al[125] suggested that in PDR development, local and systemic inflammation and endothelial impairment mutually interrelate and progress with time, as it is expressed by means of vitreous and serum VCAM-1 levels.

On the other hand, several studies question its direct implication in DR development. It has been proposed that significant and independent associations between VCAM-1 serum levels and DR prevalence do not exist, at any retinopathy stage[59,67,100,109,112], whereas Blum et al[69] demonstrated that PDR is accompanied by decreased VCAM-1 levels. Furthermore, many prospective studies rejected its involvement in DR progression or incidence[46,62,71,116]. Possible explanations for these findings include participants' better glycemic control and younger age[46,69], underlying the need for larger studies, with age and HbA1c matched participants to identify the exact role of serum VCAM-1 in DR pathogenesis.

E-selectin

E-selectin, a cell adhesion molecule and marker of endothelial function, plays a crucial role as a pro-inflammatory protein, by enhancing the adherence of leukocytes to endothelium and their transportation into the subendothelial intima[126]. Subsequently, they transform into macrophages and produce cytokines, such as IL-6 and TNF-α, which induce the hepatic CRP production[48]. E-selectin has also been recognized as an important prognostic marker for macroalbuminuria in T1DM[127].

It has been suggested that soluble E-selectin is not only associated with DR presence[128,129] but also it contributes to DR progression[71,129]. A prospective study demonstrated that E-Selectin is significantly associated with DR progression in T1DM patients, and also with the occurrence of PDR and DME[71]. More specifically, baseline E-selectin levels ≥ 40 pg/mL almost doubled the risk for PDR occurrence. Furthermore, these associations were independent of HbA1c levels, age, proteinuria, and other known RFs, supporting the hypothesis that E-selectin is involved in DR pathogenesis through a pathway at least partially independent of hyperglycemia.

On the contrary, several studies did not recognize a significant and independent association of E-selectin with DR development or progres-

sion[59,62,129]. A large prospective study by Spijkerman et al[62] in T2DM patients showed that baseline soluble E-selectin levels are not associated with DR progression independently of glycemic status. Additionally, Rajab et al[129] could not relate E-selectin baseline levels of T1DM patients and DR progression, indicating that inflammatory factors, among them E-selectin, identify DR, without contributing to its initiation or progression.

Absolute Neutrophil Count

According to Woo et al[65], Absolute Neutrophil Count (ANC) levels were strongly and independently related to both DR presence and severity. However, no association existed between ANC levels and diabetic macular edema (DME). Additionally, they demonstrated that the ratio of ANC to white blood cells (ANC/WBC) was also significantly and independently associated with DR development and progression. The ratio was not associated with diabetes, indicating that neutrophil-mediated inflammatory activity possibly plays a selective and major role in DR pathogenesis.

It has been suggested that neutrophils contribute to DR development through a Fas-Fas ligand-dependent pathway, which promotes retinal endothelial cell apoptosis and blood-retinal barrier breakdown[130]. It has not been proven though, whether the occurrence of DR follows the elevation of systemic ANC or if the chronic hyperglycemic state itself causes the ANC to rise via pro-inflammatory mediators, such as NF-κB, IL-6, and TNF-α. Therefore, further longitudinal studies are needed to identify the implication of ANC in DR pathogenesis and progression.

Fibrinogen

Fibrinogen is a hemostatic factor and an acute phase protein[131]. Its synthesis in the liver is regulated by pro-inflammatory cytokines, such as IL-6, TNF-α, and IL-1[132,133].

Numerous studies evaluated the role of plasma fibrinogen in DR development and progression with conflicting findings. Tomić et al[64] did not detect any association in T2DM patients between DR prevalence and fibrinogen levels. This suggestion was strengthened by the findings of another study[21], according to which the significant association of fibrinogen plasma levels and DR was abolished after adjustment for nephropathy status. Furthermore, no involvement of fibrinogen in DR progression in T2DM patients was detected in a prospective study[62].

On the other hand, several studies proposed that fibrinogen levels are positively related to DR prevalence in both DM types[34,66,68], while it has also been identified as an important RF for DR progression in T2DM[66]. Moreover, Le et al[68] claimed that its levels in T2DM patients are significantly and independently related to DR severity. This discrepancy could be attributed to the fact that in their study the participants were younger and no statistical analysis for glycemic control was accounted.

Homocysteine

Homocysteine plays a key role in inflammation through the activation of monocytes and the secretion of cytokines that amplify the inflammatory response[134]. More specifically, it contributes to the elevation of the proinflammatory cytokines MCP-1 and IL-8 and to leukocytes recruitment[135].

Many studies searched for a potential role of homocysteine in DR pathogenesis. Hyperhomocysteinemia was present in DR patients, however this association was not independent of albuminuria, hypothesizing that it was mediated by concurrent diabetic nephropathy[21,136,137]. On the contrary, Looker et al[137] found a significant and independent association between homocysteine levels and PDR occurrence in T2DM. Although this finding could be explained by the fact that homocysteine is a marker of impaired renal function, which is an established RF for PDR, it was suggested that homocysteine itself probably could be identified as a novel sensitive marker for PDR.

Von Willebrand Factor

Von Willebrand Factor (vWF), a blood glycoprotein with hemostatic activity, is also identified by recent studies as an inflammatory marker. It is involved in the first step of inflammation, which is the initial adhesion of platelets, providing thus a suitable surface for leukocyte recruitment[138]. Elevated vWF serum levels have been reported in both acute and chronic inflammation[139].

Many studies searched for a possible role of vWF in DR pathogenesis. No significant and independent associations were detected either in T1DM[140-142] or T2DM[113,143].

Tissue Plasminogen Activator

Tissue plasminogen activator (tPA), among its other functions, acts as a cytokine, by binding to its membrane receptors and triggering profound intracellular signaling events[144,145].

The role of circulating tPA in DR development was elaborated by several studies. None detected a positive and significant association[146,147], whereas interestingly a negative correlation between plasma tPA levels and PDR was detected in T2DM subjects[148].

Plasminogen Activator Inhibitor-1

Plasminogen activator inhibitor type-1 (PAI-1) is the major inhibitor of tPA and urokinase, playing a crucial role in the coagulation system. Its deficiency is accompanied by increased fibrinolysis and hemorrhagic diathesis[149]. It is produced by endothelium and secondarily by the adipose tissue. PAI-1 is assumed to be a significant inflammatory marker by contributing to the regulation of cytokines and cell migration[150] and by playing a key role in the obesity-induced inflammation in metabolic syndrome[151].

PAI-1 is identified as an independent predictor of T2DM incidence, probably due to the coexisting hyperglycemia, hyperinsulinemia, and hypertriglyceridemia[152-155]. As for T1DM, its association with PAI-1 is controversial[156].

The reports for a possible association between PAI-1 levels and DR in T1DM patients were also controversial[156,157]. In T2DM, PAI-1 has been identified as an independent and strong RF for DR incidence[158], especially for the most severe PDR stages[159]. More specifically, it was suggested that the risk for DR development increases by 12% for each 10 ng/dL rise in baseline PAI-1 levels[158] suggesting that the regulation of PAI-1 levels may be a therapeutic target. These associations could be attributed to the fact that elevated PAI-1 levels are accompanied by hypercoagulability, increased inflammatory activity, retinal ischemia-reperfusion injury and retinal neovascularization[158-160]. On the contrary, Le et al[68] did not find any correlation between T2DM and PAI-1 in young adults[68], while Brazionis et al[161] surprisingly demonstrated that PAI-1 has a protective role in preventing DR development.

The conflicting results might be related to differences in the methodologies of the performed studies and participants' nationalities. Whether elevated PAI-1 is a significant biomarker of endstage PDR must be testified by larger studies with subjects from different populations, to verify or reject the aforementioned hypothesis.

Serum Sialic Acid (SSA)

Serum sialic acid (SSA) is a component of cell membranes and a marker of acute phase inflammation[63]. Damage of the cell membranes, especially of vascular tissue cells, is accompanied by increased SSA levels[63]. Vascular tissue damage is also followed by ischemia, which is more significant in retinal vessels.

In DM it is associated with increased risk of cardiovascular disease, and its role in the development of diabetic microvascular complications is well established[162,163]. Nayak et al[63] found significantly elevated SSA levels in DR compared to non-DR patients, possibly because of the greater microvascular damage that occurs in DR[63].

Prostaglandins

Prostaglandins derive from arachidonic acid playing a key role in inflammation, while they may be involved in both the promotion and resolution of inflammatory activity[164]. Prostaglandin E2 (PgE2), one of the most abundant prostaglandins produced in humans, is related to inflammation, apoptosis, angiogenesis, and increasing vascular permeability[165].

Research was performed in order to study the possible role of Prostaglandin E1 (PgE1) and PgE2 in DR development in T1DM[99]. There was some evidence for the involvement of PgE2, whereas no correlation of PgE2 with DR severity was identified. As for PgE1, no association with DR was detected.

Serum Amyloid A

Serum amyloid A (SAA) is an acute phase protein, mostly synthesized in the liver under the regulation of TNF-α, IL-1, and IL-6[166]. SAA is also involved in the pro-inflammatory activity, promoting the release of cytokines.

Sharma et al[78] found that the elevated circulating levels of SAA contribute to "any stage" DR development in T1DM patients. Their findings designate further the significance of SAA as an inflammatory marker with predictive value for diabetic complications[167].

RANTES/CCL5

The chemokine RANTES/CCL5 contributes to leucocytes recruitment in inflammation, is chemotactic for eosinophils, basophils, and T-cells[168], and has angiogenic effects in several tumor model systems[169].

Meleth et al[100] found that elevated RANTES/CCL5 serum levels are strongly and positively correlated with more severe DR stages, claiming that it plays an active role in DR progression.

However, Roy et al[71] measured its circulating levels in T1DM patients, and their results dispute this association. So, its association with DR remains controversial and further studies are needed to confirm or reject it.

Stromal Cell-Derived Factor 1a/ CXCL12

Stromal cell-derived factor 1a (SDF-1a)/CXCL12 is a chemokine which is strongly chemotactic for lymphocytes and stimulates intracellular signaling and chemotaxis in retinal pigment epithelium cells[170,171]. SDF-1a receptor is the most common chemokine receptor expressed on inflammatory cells[172]. It also plays a key role in neovascularization, by elevating and promoting angiogenesis in hypoxia[174]. Furthermore, its involvement in trafficking and migration of autoreactive B cells possibly contributes to DM development[175].

Several studies[71,100,172] investigated its potential participation in DR development with inconsistent results. An indirect link between DR and circulating SDF-1a exists, as it is strongly associated with important processes of DR pathogenesis[172]. Moreover, higher serum levels are present in patients with more ischemic DR forms[100], suggesting a role in DR development. However, its role in DR progression remains doubtful after a recent study[71].

Progranulin

Progranulin is a significant molecule that is involved in the insulin signaling pathway and is identified as a novel marker of chronic subclinical inflammation in T2DM[176].

Xu et al[81] investigated the potent associations between circulating progranulin and DR in T2DM patients, proposing that progranulin could be regarded as a marker of DR severity, since its serum levels were significantly higher in PDR patients compared to those with less severe DR stages.

YKL-40

YKL-40, a new marker of acute and chronic inflammation, is involved in endothelial dysfunction, and is expressed in macrophages and smooth muscle cells[177]. YKL-40 is related to microalbuminuria in DM[178,179].

Aguilera et al[82] searched for a possible role of YKL-40 in DR development, without detecting any association, indicating that more studies are needed in order to confirm or reject its involvement in DR pathogenesis.

Conclusions

DR remains a global health issue with great socioeconomic impact. The established RFs only partially explain its pathogenic mechanisms, and thus it is significant to further understand through which pathways the disease develops and progresses to more severe and visual-threatening stages.

With this review, we tried to shed new light on the possible existing connection between systematic inflammation and DR and recognize the systemic biomarkers with the most important role. The performed investigations demonstrated a role for inflammation, however a bit controversial results in several occasions indicated that it remains unclear whether systemic inflammation is independently involved in the pathogenesis of retinopathy or if it is just a disease indicator. Furthermore, we highlighted the predictive value of many inflammatory biomarkers in early detection of the diabetic subjects at high risk for developing DR, suggesting that inflammatory activity could be regarded as a useful and an inexpensive tool for screening the diabetic patients contributing to the prevention of progression to more severe stages.

Further research is required to test the exact implication of inflammation in DR, while future studies comparing the vitreous and systemic inflammatory activity in the pathogenesis of the disease are needed in order to verify the role of systemic inflammation. A confirmation of the aforementioned hypothesis would provide new data in the challenge of developing the suitable medication that could ameliorate DR severity levels.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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