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Review article

Role of inflammation in diabetic macular edema and neovascular age-related macular degeneration

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ABSTRACT

Diabetic macular edema (DME) and neovascular age-related macular degeneration (nAMD) are multifactorial disorders that affect the macula and cause significant vision loss. Although inflammation and neoangiogenesis are hallmarks of DME and nAMD, respectively, they share some biochemical mediators. While inflammation is a trigger for the processes that lead to the development of DME, in nAMD inflammation seems to be the consequence of retinal pigment epithelium and Bruch membrane alterations. These pathophysiologic differences may be the key issue that justifies the difference in treatment strategies. Vascular endothelial growth factor inhibitors have changed the treatment of both diseases, however, many patients with DME fail to achieve the established therapeutic goals. From a clinical perspective, targeting inflammatory pathways with intravitreal corticosteroids has been proven to be effective in patients with DME. On the contrary, the clinical relevance of addressing inflammation in patients with nAMD has not been proven yet. We explore the role and implication of inflammation in the development of nAMD and DME and its therapeutical relevance.

1. Introduction

The increase in life expectancy, as well as changes in life habits, has led to an increase in the prevalence of chronic inflammatory eye disorders such as chorioretinal degenerative diseases.[110]

Among patients with diabetes mellitus (DM), diabetic retinopathy (DR) and diabetic macular edema (DME) are the most common complications leading to vision loss.[182] It was estimated that 103.1 million, 28.5 million, and 18.8 million people worldwide were diagnosed with DR, vision-threatening DR, and DME, respectively, in 2020;[207] with a likely increase in 2030 to 129.84 million for DR, 44.82 million for vision-threatening DR and 23.50 million for DME.[186] A systematic review and meta-analysis published recently found that the prevalence of DME was 5.47 % in the overall sample, ranging from 5.81 % to 5.14 % in the low- and high-income countries, respectively.[74]

Along with DR and DME, neovascular age-related macular degeneration (nAMD) is an exudative chorioretinopathy that causes severe visual impairment in older adult patients worldwide.[26,74,75,209]

The estimated total prevalence of age-related macular degeneration (AMD) in 2020 was projected to be 196 million people, increasing to 288 million in 2040. Of those, nAMD represents approximately 10–15 %, and about 20 million people were affected in 2020. Due mainly to its rapid progression, it represents 90 % of severe vision loss associated with macular degeneration.[26,74,110,209]

Although DR/DME and nAMD are multifactorial disorders, current scientific evidence highlights a key role for several common cellular and molecular events: vascular endothelial dysfunction, [62,212]increased vascular permeability, [139,169]oxidative stress, [12,15,46,113]overexpression of adhesion molecules, [46,90] alterations in the extracellular matrix (ECM) metalloproteinase system,[63,83,84,131] and increased levels and activity of pro-inflammatory molecules.[23,35,47,50,52,65,81,163,168]

On the other hand, inflammation, a nonspecific protective response,

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that aims to neutralize harmful stimuli, interacts with vascular changes, but the nature of this interrelationship frequently remains complex and puzzling, and the consequences are difficult to predict. [35,157] Moreover, inflammation and angiogenesis can be triggered by the same molecular events, in which ischemia plays an important role, further strengthening this association. [32,170] We review the role of inflammation in the development of DME and nAMD and its therapeutic relevance.

2. Methods

A comprehensive narrative review of the available evidence was performed. We carried out literature research using the following keywords: "Diabetic Macular Edema" AND "Inflammation" OR "Neurovascular Unit" AND "Clinical Outcomes"; "Diabetic retinopathy" AND "Neurovascular Unit" AND "Clinical outcomes"; "Neovascular age-related macular degeneration" AND "Inflammation" OR "Complement system" AND "Clinical outcomes". This study included papers conducted on humans and written in English, French, Italian, Portuguese, or Spanish. In addition, we manually checked the reference lists of the different studies included in this review to find any additional publications that could be useful for the current paper.

3. Diabetic macular edema

3.1. The role of the retinal neurovascular unit in DR and DME

In patients with DM, the dysregulation of glucose and lipid metabolism has marked effects on both retinal cells and vessel endothelium. Extensive research, comprising both *in vivo* and *in vitro* experiments, has demonstrated loss of endothelial cells and pericytes following exposure to elevated glucose levels. [105,112] Moreover, alterations in retinal vessel endothelium serve as chemotactic signals for leukocyte adhesion, perpetuating a cycle of chronic inflammation. Simultaneously, abnormal blood flow patterns within the retina manifest as microaneurysms, capillary depletion, and retinal ischemia.[47]

The pathogenesis of diabetes complications is commonly analyzed within the context of cellular metabolic and signaling pathways that contribute to organ dysfunction, and specifically for DR/DME development the blood-retinal barrier (BRB) plays a crucial role. Its structural foundation lies in neurovascular units (NVU), which exemplify a collaborative relationship between the nervous and vascular systems, supporting each other's functions.[193]

The NVU is a complex multi-heterocellular structure composed of endothelial cells, neurons, glia, smooth muscle cells, pericytes, and extracellular matrix (Table 1). Together with the BRB, the NVU, regulates blood flow and retinal cell metabolism, thus allowing the controlled exchange of nutrients and metabolic waste products.[45,61, 96, 102,106,126,150,193,210]

Cellular alterations in the retinal NVU, including changes in the cytoskeleton, metabolism, chaperones, secreted proteins, signaling proteins, and transporters, play an important role in the development and progression of DR and DME.[102,106,130,137,159] Early activation of the innate immune system, the complement system, and retinal microglia have a role in the damage of the retinal NVU causing reduced synaptic protein expression and altered glial function.[103,107,119,155]

According to current evidence, DR is not only a microvascular complication due to DM, but also a neurodegenerative disease.[32] Glial cells (astrocytes, Müller cells, and resident microglia) are critically located between the vasculature and neurons of the retina, regulating the retinal microenvironment, which is compromised in the initial stages of DR.[32,170]

Müller cells and astrocytes play a crucial role in actively maintaining retinal homeostasis and protection against oxidative stress.[202] Müller cells, spanning the entire thickness of the neural retina, provide structural and metabolic support to all neuronal cells and contribute to local immune surveillance as well. They produce interleukins (ILs), chemokines, and vascular endothelial growth factor (VEGF). Furthermore, Müller cells regulate the expression of aquaporins and inwardly rectifying potassium (Kir) channels which are essential for maintaining fluid homeostasis.[25,50,81,84,163]

Resident microglial cells respond to chronic insults, such as diabetes, by becoming activated, changing their appearance into an ameboid form, and gaining the ability to migrate into the retina.[23] Once activated, microglia produce proinflammatory and cytotoxic factors, including tumor necrosis factor (TNF)-alpha, IL-a1ß, reactive oxygen species (ROS), and reactive nitrogen species.[182] These factors functionally impair neuronal cells and cause injury to pericytes and endothelial cells, leading to dysfunction of the NVU, BRB breakdown, increased vascular leakage, transcellular transport, immune cell infiltration, and reduction of the intercellular junction, finally resulting in the development of DME.[130,137,159]

Table 1
Different components of the Neurovascular Unit (NVU) and their function.

Component	Function
Endothelial cells (ECs)	• Their specialization depends on the vascular bed in which they are situated. • At the BRB: • ECs exhibit reduced pinocytosis/transcytosis. • Increase expression of tight junction molecules. • Exclude free transport of substances over 400 kDa
Mural cells[a]	• They are positioned in the basement membrane shared with ECs. • They are involved in: • Maintain vascular stability. • Provide structural support for blood vessels. • Govern vasodilation/constriction.
Glial cells	• Glial cells physically ensheath blood vessels with their endfeet, creating the semi-permeable glia limitans. • Glia physically connects vessels to neurons; modulates neurotransmission; and impacts neurogenesis.
Microglia; Macrophages; and Perivascular Macrophages.	• They play roles in phagocytosis and the inflammatory response.
ECM molecules	• They support the glio-vascular interface.

ECs: Endothelial cells; BRB: Blood retinal barrier; ECM: Extracellular matrix cells.
[a]Constitute pericytes and vascular smooth muscle cells (vSMCs).
Source:Adapted from Kugler et al (102.

3.2. The advanced glycation end products (AGEs), protein kinase C (PKC) and polyol pathway

In patients with DM, hyperglycemia can induce the overactivation of multiple biochemical pathways, including the advanced glycation end products (AGEs), the polyol, the PKC activation, the local renin-angiotensin system (RAS), and the hexosamine pathways.[11,35,155]

Overactivation of these pathways induces inflammation, hypoxia, and oxidative stress[35,192] which in turn leads to a BRB breakdown, increasing osmotic pressure with the subsequent edema.[35,192]

AGEs are biological macromolecules (proteins, lipids, or DNA) that become glycated after exposure to glucose.[177] AGEs enhance fibrosis and trigger inflammation by forming collagen crosslinks and engaging with the AGE receptor (RAGE), which disrupts calcium regulation.[35] Additionally, they have been associated with leukocyte activation, and promote the upregulation of the vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) on the endothelial cell surface.[28] AGEs can bind various receptors on the cell surface and stimulate the production of reactive species of oxygen, the increase of cell permeability, and inflammation.[24,73]

The activation of the polyol pathway leads to alternative glycolysis through sorbitol and fructose production,[18,188] and overexpression of ROS, with the subsequent increase of cell oxidative stress.[33] On the other

hand, the accumulation of fructose, which is considered a glycating agent, is responsible for the formation of AGEs.[33]

Finally, hyperglycemia also causes the accumulation of diacylglycerol (DAG) in the retina, which is responsible for the PKC activation pathway.[35,177] This is involved in different processes related to DME, such as retinal vascular dysfunction and pericyte loss[55,64], induction of angiogenesis and leukocyte adhesion[2189], increase of oxidative stress levels[55] and apoptosis.[10]

3.3. The role of inflammation in DME

Inflammatory processes may underlie many of the retinal vasculature alterations observed in eyes with DME.[81] Several cytokines, chemokines, and permeating factors [including placental growth factor (PLGF), platelet-derived growth factor (PDGF), interleukin (IL)−6, IL-8, monocyte chemoattractant protein (MCP)−1, ICAM-1, interferon-inducible 10-kDa protein (IP-10) and erythropoietin (EPO)] have been repeatedly found elevated in ocular fluids of eyes with DME (Table 2). A relationship between intraocular levels of inflammatory molecules and retinal thickness at the OCT has been found.[47,50,51, 97,107,132,133,143,146, 213]

Ischemic retina releases vascular endothelial growth factor (VEGF), which may trigger to neo-angiogenesis but also causes excessive vascular permeability[204,208]. Its family includes several VEGF isoforms (-A, -B, -C, -D, -E) and the PLGF. The overexpression of VEGF-A and PLGF are associated with an increase in vascular permeability[35,208] and

Table 2
Different inflammatory/ pro-inflammatory molecules related to diabetic retinopathy (DR) and diabetic Macular Edema (DME) and its relationship with central retinal thickness (CRT).

Molecules	Ocular media	Increase*	CRT (±)	Ref.
IL−3	Aqueous	3.6 ×	-	79
	Vitreous	NS[a]	-	56
IL−6	Aqueous	10.4 ×	-	79
	Vitreous	19.8 ×	-	51
	Vitreous	10.2 ×	Yes (+)	50
	Vitreous	14.4 ×	-	213
	Aqueous	2.3 ×	No	107
		NS[a]	-	56
IL−8	Aqueous	10.3 ×	-	79
	Vitreous	8.9 ×	-	213
	Aqueous	2.3 ×	Yes (+)	107
	Vitreous	NS[a]	-	51
IL−13	Aqueous	0.9 ×	No	107
	Vitreous	NS[a]	-	51
EGF	Aqueous	1.7 ×	-	79
	Vitreous	NS	-	213
	Aqueous	NS	No	107
	Vitreous	NS[a]	-	56
HGF	Aqueous	1.9 ×	-	79
	Vitreous	3.6 ×	-	143

aMultivariate analysis with adjustment on all biological factors assessed.
* Fold increase Patients vs Controls.
(+) = positive correlation with central macular thickness.
(−) = negative correlation with central macular thickness.
Abbreviations: CFRT: Central retinal thickness; IL: Interleukin; EGF: Epidermal Growth Factor; HGF: Hepatocyte Growth Factor; TGF-β: Transforming Growth Factor β; TNF-α: Tumor Necrosis Factor α; PGF: Placental Growth Factor; VEGF: Vascular Endothelial Growth Factor; PEDF: Pigment Epithelium Derived Factor; PDGF-AA: Platelet Derived Growth Factor; PDGF-AB: Platelet Derived Growth Factor; PDGF-BB: Platelet Derived Growth Factor; ICAM-CD54: InterCellular Adhesion Molecule 1; VCAM: Vascular cell adhesion molecule 1; CXCL-10: C-X-C motif chemokine 10; IP-10: Interferon gamma-induced protein 10; CCL2: Chemokine ligand 2; MCP-1: Monocyte chimoattractant protein 1; CXCL-9: C-X-C motif chemokine ligand 9; MIG: Monokine induced by γ-interferon; MMP-9: Matrix metallopeptidase 9; PAI-1: Plasminogen activator inhibitor-1; sF1t1: Soluble fms-like tyrosine kinase-1; sVEGFR-1 = Soluble vascular endothelial growth factor receptor 1; NS: Not significant.
Source:Adapted from Daruich et al (35.

are elevated in the retina and vitreous of patients with DME;[81] however, in DME eyes that do not adequately responding to VEGF inhibitors (anti-VEGF) treatment, higher levels of inflammatory molecules, such as IL-6, IL-8, tumor necrosis factor receptor (TNFR)−1 and −2, and matrix metalloproteinase (MMP)−9 were documented.[190]

Increased levels of inflammatory cytokines, including TNF-α, IL-1β, and IL-6, favor the upregulation of intracellular adhesion molecules, such as ICAM-1 and VCAM-1, which attract monocytes and leukocytes and promote a continuous inflammatory response[132,133,140,177]. Finally, the combined action of these processes results in decreasing local blood flow velocity, further increasing retinal hypoxia[132,133].

Fig. 1 summarizes the main pathways involved in the development of DR and DME.

4. Neovascular age-related macular degeneration

The pathophysiology of AMD is multifactorial and includes defects in autophagy, mitochondrial dysfunction with altered response to oxidative stress, changes in the extracellular matrix metalloproteinase (ECM) system, aging of the choroidal vascularization and chronic inflammation.[6,46,53,83,84,86,185]

Early and intermediate stages of AMD are usually characterized by the presence of drusen, which are deposits of ECM beneath the basal lamina of the RPE.[6,16,53]

Intermediate AMD can evolve to more advanced stages that include 2 different forms, not mutually exclusive, namely geographic atrophy and nAMD. [6,16,53]

The hallmark of nAMD is the development of macular neovascularization (MNV). Hypoxia, as well as hyperactivity of the complement system, leads to disturbances in the pro/antiangiogenic balance in RPE cells. Overexpression of proangiogenic VEGF contributes to the breakdown of the BRB and sprouting of fragile blood vessels from the choroid through Bruch membrane into the retina;[15,110] however, VEGF alone is not sufficient to cause MNV, indicating the involvement of other pathways, such as components of the alternative complement pathway (ACP)[135] and inflammation.[6,16,53,86, 138,164,185]

4.1. Complement system and glial-mediated mechanisms in nAMD

The complement system is composed of approximately 50 proteins, circulating in the blood as inactive components, whose main role is to recognize and mediate the removal of pathogens, debris, and dead cells.[29,152] In nAMD, complement activation leads to the recruitment and activation of immune cells, including retinal microglial cells, circulating lymphocytes and monocytes/macrophages, and mast cells.[14, 136] Moreover, complement activation can also stimulate RPE cells into secreting a range of inflammatory cytokines, such as IL-6, IL-8, and monocyte chemotactic protein-1 (MCP-1), further contributing to BRBs dysfunction.[113]

Drusen contain many components of the ACP, such as C3/C5, complement factor H (CFH), and the terminal pathway proteins C5, C6, C7, C8, C9[76,156]. Anaphylatoxins C3a and C5a, generated with the breakdown of C3 and C5, were immunolocalized to drusen in eyes with nAMD, providing direct evidence of complement activation.[135] Furthermore, C3a, C5a, and membrane attack complexes found in subretinal drusen plaques are associated with an increase in the levels of the pro-angiogenic VEGF in primary human RPE cells, but not in human choroidal endothelial cells.[36,76,78, 111,135,156,168,187] In nAMD, the stimulation of monocytes by C3a can lead to IL-1β secretion and leucine-rich repeat (LRR)-containing proteins (NLR) P3 (NLRP3) inflammasome activation[8,9], and both C3a and C5a cause an increase in nuclear factor kappa B (NF-kB) signaling in monocyte-derived dendritic cells.[8,109] Additionally, these ACP components and the membrane-attack-complex (MAC) C5b-9 in RPE cells overlying drusen, may either lyse RPE cells or impair their physiological homeostasis.[36,76,78, 111,135,156,168,187]

In this complex environment, retinal microglia have been implicated

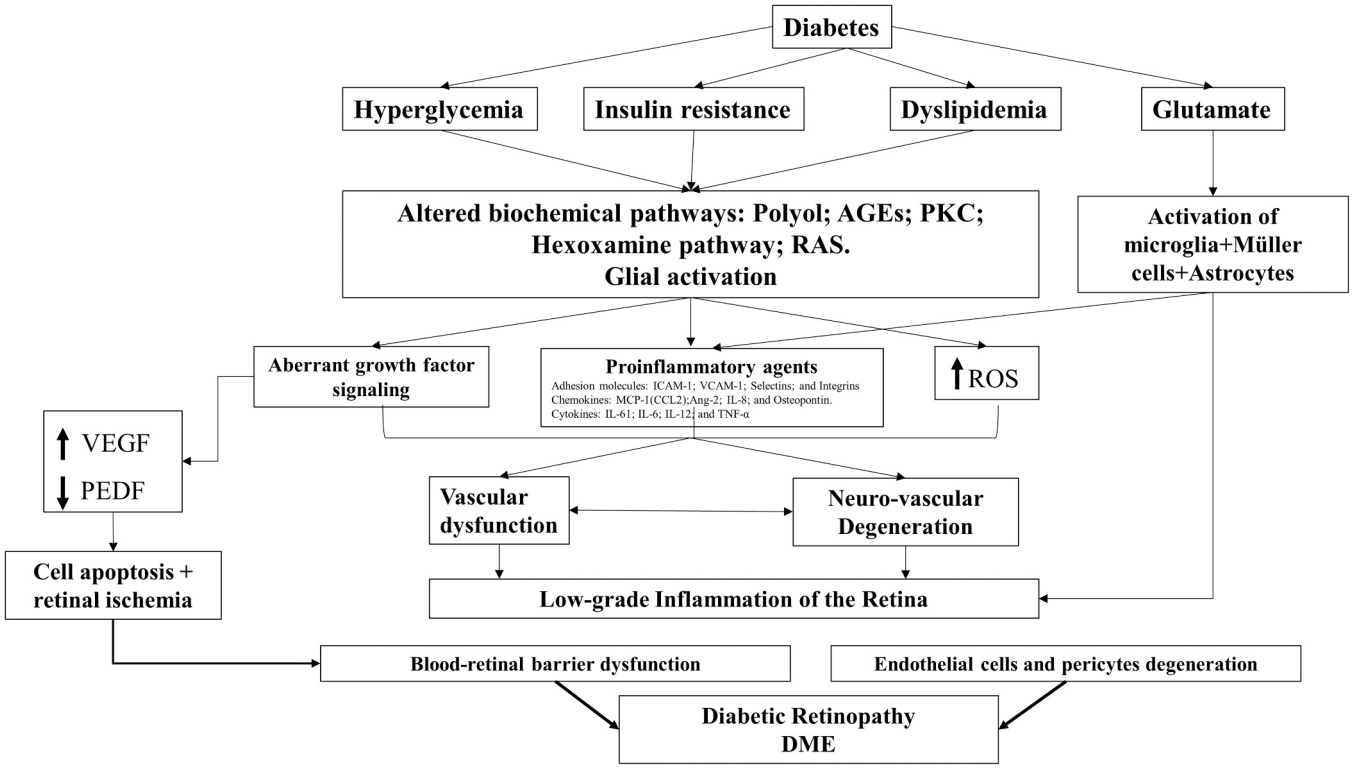

Fig. 1. An overview of the different pathways involved in the development of diabetic retinopathy (DR) and diabetic Macular Edema (DME). Adapted from Daruich et al (35) and Romero-Aroca et al (155). LDL: Low-density lipoprotein; ROS: Reactive oxidative species; AGEs: Advanced glycation end-products; PKC: Protein kinase C; RAS: Renin–angiotensin system; ICAM-1: Inflammatory intercellular adhesion molecule-1; VEGF: Vascular endothelial growth factor; VCAM-1: Vascular cell adhesion molecule-1; PEDF: Pigment epithelium-derived factor; CCL2: Chemokine C-C motif ligand 2; Ang-2: angiopoietin-2; IL: Interleukin; TNF: Tumor necrosis factor; DME: Diabetic Macular Edema.

in the etiology of nAMD. Retinal microglia are found able to produce and release ACP components, such as C3, CHF, and complement factor B (CFB).[44] Since the link has been established between alterations in the ACP, microglia, and the risk of developing nAMD,[8,9,44,49,53,66,76,78, 109, 111,129,156,158] there is increasing evidence suggesting the involvement of inflammation and dysregulated innate immunity in the pathogenesis of nAMD.[6149,164]

4.2. *The role of inflammation in nAMD*

RPE and dendritic cells (DCs) play crucial roles in the formation of drusen. Choroidal DCs become activated and recruited in response to damaged RPE cells. This activation perpetuates and amplifies local inflammation through various mechanisms, including the formation of immune complexes and the activation of complement and choroidal T-cells or phagocytic cells.[66,78,87]

Furthermore, in addition to the ACP components, drusen contain several pro-inflammatory factors, such as proinflammatory cytokines (IL-6, IL-18, IL-22, and IL-17A), matrix-remodeling proteases (MMP) (mainly MMP-1, MMP-2, MMP3, and MMP-9), and growth factors (e.g., transforming growth factor-β).[36,76, 111,135,156]

Pathological changes within the Bruch membrane combined with proangiogenic and inflammatory factors enable the invasion of endothelial cells, pericytes, fibrocytes, and inflammatory cells into the sub-RPE or the neurosensory retina.[131,171] Subsequently, there is an active inflammatory phase, in which several mediators are produced by the RPE, retinal glial cells (Müller cells and microglia), endothelial cells, and invading macrophages.[16,36,76,111,156] IL-1β, for instance, produced by activated retinal microglia and RPE[118,175] stimulates VEGF secretion[86] and may initiate a paracrine amplification loop of inflammasome activation.[20]

Additionally, activated components of the ACP (such as C3a and C5a) and CFH, significantly increase oxidative stress in the retina, leading to the excessive formation of ROS.[17] In patients with nAMD, the existence of significantly increased levels of total oxidant status in the serum and decreased levels of total antioxidant status has been reported.[39,148] ROS are associated with nAMD progression since able to induce necrosis of RPE cells, promoting the release of damage-associated molecules that can further stimulate immune and inflammatory responses.[148]

Collectively, damage to the RPE and Bruch membrane breakdown leads to the activation of inflammatory pathways resulting in the release of proinflammatory cytokines and other mediators.[7,37,38,80,86,95,100,134, 162] This environment promotes the activation of immune cells (granulocytes, monocyte-derived macrophages, and lymphocytes) and complement system,[67,70] which stimulates RPE cells to release IL-8, and MCP-1, further contributing to BRB dysfunction.[119] Fig. 2 summarizes the different pathways involved in the pathophysiology of nAMD.

5. Therapeutic relevance of inflammation in DME and nAMD

Neovascular AMD and DME are 2 prevalent and disabling macular disorders, with complex and, not fully-understood etiopathogenesis. The advent of anti-VEGF therapy meant a significant treatment improvement, but many patients failed to achieve the established therapeutic goals.[165,166] Up to 40 % of eyes with DME treated with anti-VEGF do not adequately respond to treatment.[21,59] Whereas in nAMD, despite great short-term functional and anatomical results, long-term observational studies revealed that almost one-third of patients had poor visual outcomes over periods of several years,[22 101,125,154,167]. These findings might indicate a complex pathophysiology, in which other factors, such as inflammation, are involved in the development and progression, at least for DME;[6,35,53,81,86,98,171] however, it must be considered that vision loss in nAMD may be related to other factors, such as retinal

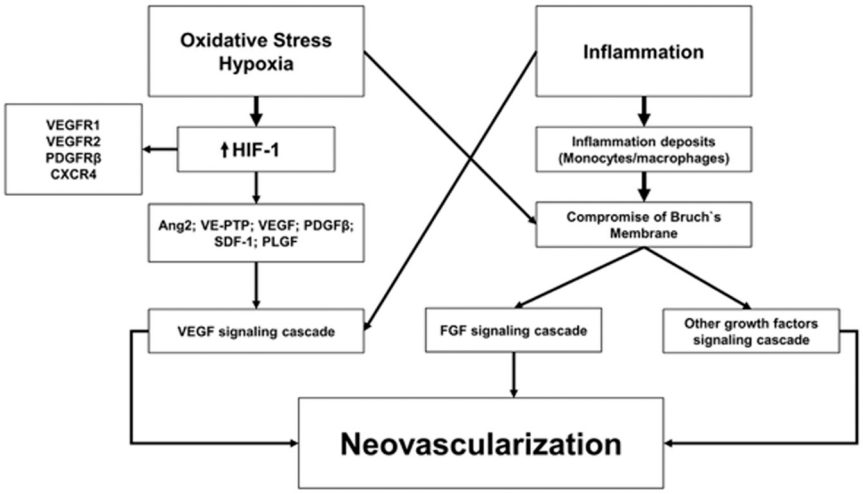

Fig. 2. Overview of the pathophysiological leading to choroidal neovascularization. Adapted from Anderson et al (7) and Campochiaro (26). Ang-2: Angiopoietin-2; CXCR4: CXC chemokine receptor 4; FGF: Fibroblast growth factor; HIF-1: Hypoxia-inducible factor-1; PDGFβ: Platelet-derived growth factor; PDGFRβ: platelet-derived growth factor receptor beta; PLGF: Placental growth factor; SDF-1: stromal derived factor-1; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; VE-PTP: Vascular endothelial protein tyrosine phosphatase.

degeneration, fibrosis, and/or atrophy.[6,53,86]

As inflammation is a key contributing factor in the etiopathogenesis of DME, research on corticosteroids (CS), has been ongoing for many years due to their powerful anti-inflammatory/antiedematous effects, with different intravitreal CS nowadays approved.[19,34,184,206] CS inhibits the arachidonic acid pathway via phospholipase A2 inhibition, this reduces the synthesis of thromboxane, leukotrienes, and prostaglandins. Furthermore, CS can stabilize lysozymes, decrease the synthesis of inflammatory mediators and VEGF, inhibit cell proliferation, stabilize the BRB, enhance the density and activity of tight junctions in the retinal capillary endothelium, and improve retinal oxygenation.[153,179] In addition, there is evidence suggesting that CS controls gene expression promoting anti-inflammatory factors.[160]

Clinical studies reported that intravitreal injection of CS significantly decrease the levels of monocyte chemo-attractant protein 1 (MCP-1), soluble intercellular adhesion molecule 1 (sICAM-1), monokine induced by gamma interferon (MIG), soluble vascular cell adhesion protein (sVCAM), IL-6, interferon-induced protein (IP)−10, VEGF, and PDGF.[145,173] Furthermore, more pronounced changes in specific inflammatory OCT imaging biomarkers in the inner retina are documented after CS versus anti-VEGF treatment.[116,124,183,195,198,199,201] The evaluation of OCT imaging biomarkers is far less invasive than molecular biomarkers found in the aqueous humor[196,197] and are classified as disorganization of the inner retinal layers (DRIL),[122] presence, size, and localization of hyperreflective foci (HRF),[123] serous retinal neuroepithelial detachment (SRD),[200] intraretinal cystoid spaces,[117] loss of integrity of the outer retinal layers, specifically the external zone/external limiting membrane (EZ/ELM).[89] Imaging biomarkers may have a predictive/prognostic role in DME[121,183] and support precise clinical management by identifying inflammatory DME phenotypes.[201] Specifically, SRD is associated with an elevated vitreous concentration of proinflammatory cytokines, such as interleukin-6 and interleukin-8,[174] whereas HRF represents activated microglia and may serve as a surrogate marker chronic neuro-inflammation.[116,124,183,195,198,201]

Their routine analysis and management in daily practice can be extremely complex due to the large amount of data generated and the time needed for manual identification [1,120]. Some AI algorithms have been shown to be useful, reliable, and reproducible tools for assessing the most relevant OCT imaging biomarkers.[124,181] They may allow clinicians to routinely identify and quantify these parameters, offering an objective way to phenotype DME.[114]

Unlike DME and DR, where inflammation holds a pivotal role since the initial stages of the disease[5,46,50,65,81,88,163,168], in nAMD, inflammation seems to be related to the presence of drusen. They act as triggers that can activate different pathways that promote the progression of AMD to the late stage.[16,78,156]

Few reports are published on the use of intravitreal CS in addition to anti-VEGF for patients with nAMD [31,40,42]. The administration of intravitreal CS has reduced the central retinal thickness and the number of anti-VEGF injections in the long term, but has not led to functional improvements.[13,40,57]

Local inhibition of complement activation has been considered a promising approach not only for geographic atrophy (GA)[69,93] but also for treating nAMD. [78,142,161] New biologic agents included molecules that target different components of the complement cascade, such as C3-mediated treatments (POT-4/AL78898A, APL-2); factor D-mediated treatments (lampalizumab); and C5-mediated treatments (eculizumab, LFG316, ARC1905).[141] Despite the preclinical relevance of the complement pathway, none of these molecules moved to the phase III stage of development in nAMD. Additionally, results from pivotal trials of complement inhibitors in GA[69,93] have shown an increased incidence of macular neovascularization in the treatment group compared with sham, highlighting the complement system's complex and not fully understood role in the pathogenesis, and as a therapeutic target, in nAMD.[142,205]

It is worth mentioning an additional pathway that has been recently explored as a potential target in DME and nAMD, which is the angiopoietin-Tie2 (Ang/Tie2) axis.[94] Ang/Tie2 pathway is involved in distinct and important stages of angiogenesis such as vessel remodeling/maturation and vascular permeability with a possible downstream effect that may impact the underlying inflammation.[95]

Due to the failure of complement inhibitors monotherapy trials, there are no available treatments that directly and specifically tackle the complement system/inflammation in nAMD, and all the therapeutic agents target VEGF.[151,161] With the latest approved drugs to have either a higher molar dose [104] or the capability to target and inhibit both VEGF and Ang-2;[92] this in turn leads to longer treatment intervals and better anatomical results when compared to older anti-VEGF.[211]

On the contrary, since we have better understood the role of inflammation in the development and progression of DME the rationale for CS employment has improved. Different meta-analyses have evaluated or compared the effect of anti-VEGF therapy and CS in patients with DME.[4,30,43,68, 103,108,144,147,153,194,203] A systematic review and meta-analysis that included 14 randomized controlled trials (RCTs)

assessed the efficacy and safety of intravitreal CS compared with anti-VEGF in patients with DME.[144] Regarding visual function, at the last follow-up visit, there were no significant differences in best-corrected visual acuity between the eyes treated with intravitreal CS and those treated with intravitreal anti-VEGF (weighted mean difference: −0.00 ETDRS letters; 95 % confidence interval: −0.05 to 0.04 ETDRS letters; p = 0.91).[144] Nevertheless, among the 12 RCTs that reported information about retinal thickness, final retinal thickness was significantly lower in the eyes treated with intravitreal CS than in those treated with intravitreal anti-VEGF (weighted mean difference: 39.99 μm; 95 % confidence interval: 14.58 μm to 65.41 μm; p = 0.002).[144]

Chi and coworkers, in a systematic review and meta-analysis, evaluated not only RCTs, but also real-world studies.[30] In patients with resistant DME, defined as DME with suboptimal response after anti-VEGF injections, best-corrected visual acuity was better in the eyes treated with CS than in those treated with anti-VEGF (mean difference: 0.12 logMAR, 95 % CI 0.02–0.21, I2 = 0 %). Nevertheless, in patients with nonresistant DME, a nonsignificant difference was found in visual outcomes between intravitreal CS and intravitreal anti-VEGF (mean difference: 0.00 logMAR; 95 % confidence interval: −0.06 to 0.05).[30] Regarding anatomic outcomes, intravitreal corticosteroids achieved a greater retinal thickness decrease than anti-VEGF in both groups.[30]

Despite those results, CS has been long associated with a higher incidence of intraocular pressure-related adverse events which represent the main limitations and challenges of these anti-inflammatory drugs. The results of a retrospective multicenter analysis, which included data from 3014 CS injections in 1434 eyes with DME, found that 271 eyes required cataract surgery.[147] Regarding intraocular pressure-related adverse events, 285 eyes had an intraocular pressure rise. Among them, 15 eyes did not require any intraocular pressure lowering treatment, 260 eyes were successfully managed with topical ocular hypotensive medication, 1 eye was treated with laser trabeculoplasty, and 9 eyes required surgery.[147]

Development and progression of cataracts have also been associated with prolonged and repeated exposure to CS, although according to the results of a meta-analysis comparing the outcomes of cataract surgery combined with either anti-VEGF therapy or CS in patients with DME, the latter provided better anatomic outcomes than anti-VEGF.[43]

It is becoming increasingly important to define the patients' characteristics that may guide the choice among anti-VEGF and CS treatments in first-line settings and different international guidelines and consensus documents have been published trying to solve this issue.[54,58,99,166,176,191] Additionally, recent prospective and retrospective studies highlight that early-switch to CS (after 3–6 anti-VEGF injections) had better best-corrected visual acuity than late-switch patients (after >6 anti-VEGF injections) despite both groups showing significant central subfield retinal thickness (CRT) improvement.[71,127] This is of particular interest as patient management strategies may also include switching from one agent to another in case of refractory eyes; due to the main use of anti-VEGF as a front-line drug, a therapeutic switch to CS is the most common practice.[166]

5.1. Novel therapeutic options in development for DME and wAMD

Novel molecules are currently under development for DME and nAMD; herein we describe a selected list of drugs that target pathways different than VEGF.[27,41,48,60,77,82,85, 91,117,172,178,180] (Table 3).

As there has been an increased interest in the inflammatory mechanisms behind the pathogenesis of DME, a range of new drugs are currently being evaluated. These include novel CS formulations, fusion protein targeting VEGF and integrin, interleukin-6 inhibitor; endothelin pathways targets, guanylate cyclase activator– as well as inhibitors of connexin43, plasma kallikrein inhibitor, rho-associated protein kinase 1 and 2, and reduction-oxidation factor-1.[48,172]

Additionally, the route of administration for these new therapies can be topical (OCS-01 and OTT-166), oral (Tonabersat, RZ402, OPL-0401, APX-3330, Runcaciguat, and AKST4290), intravitreal (AG73305, R07200220, Perfuse-01, IBE-814 IVT, and SOM-401), or suprachoroidal (OXU-001).[27,41,48,60,77,82,85, 91,117,172,178,180]

The topical dexamethasone ophthalmic suspension OCS-01(Oculis

Table 3
Overview of the current phase 2 and 3 clinical trials in diabetic eye diseases and neovascular age-related macular degeneration.

Drug	Diabetic Eye Diseases Condition	Mechanism	Delivery	NCT	Status	Last update
OCS−01	DME	Steroid, Dexamethasone	Topical drop	NCT05066997	Active, not recruiting	January 2023
AG73305	DME	Fusion protein targeting VEGF and integrin	Intravitreal injection	NCT053001751	Recruiting	July 203
R07200220	DME	Interleukin−6 inhibitor	Intravitreal injection	NCT05151731	Recruiting	September 2023
Perfuse−011	NPDR	Targets endothelin pathways	Intravitreal implant	NCT06003751	Recruiting	August 2023
OXU−001	DME	Steroid microspheres. Microcatheterization device	Suprachoroidal	NCT05697809	Recruiting	July 2023
Tonabersat	DME	Connexin43 inhibitor	Oral	NCT05727891	Recruiting	August 2023
RZ402	DME	Plasma kallikrein inhibitor	Oral	NCT05712720	Recruiting	March 2023
OPL−0401	NPDR, mild PDR	ROCK 1 and 2 inhibitor	Oral	NCT05393284	Recruiting	April 2023
APX−3330	NPDR, mild PDR	Ref−1 inhibitor	Oral	NCT04692688	Completed	February 2023
Runcaciguat	NPDR	Soluble guanylate cyclase activator	Oral	NCT04722991	Active, not recruiting	September 2023
OTT−166	NPDR, mild PDR	Integrin inhibitor	Topical drops	NCT05409235	Active, not recruiting	September 2023
IBE−814 IVT	DME	Steroid, Dexamethasone	Intravitreal implant	NCT04576689	Active, not recruiting	March 2023
SOM−401	DME	Nucleoside reverse transcriptase inhibitor	Intravitreal injection	NCT05699759	Recruiting	March 2023
Neovascular Age-related macular degeneration						
Drug	**Condition**	**Mechanism**	**Delivery**	**NCT**	**Status**	**Last update**
IBI−302	nAMD	Bispecific fusion protein	Intravitreal injection	NCT05972473 NCT05403749	Not yet recruiting	August 2023 June 2022
AKST4290	nAMD	CCR3 inhibitor	Oral	NCT04331730	Completed	October 2022

NCT: Number of clinical trial; DME: Diabetic Macular Edema; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; ROCK: Rho-associated protein kinase; Ref: Reduction-oxidation factor; nAMD: Neovascular age-related macular degeneration.
Source:Adapted from Fowler et al (48) and Jung & Rachitskaya (82.

SA, Lausanne, Switzerland), exploits the use of nanoparticle aggregates based on γ-cyclodextrin to enhance drug penetration into both the anterior and posterior segments of the eye. In a multicenter, double-masked, parallel-group, randomized, phase 2 study, has been shown to be significantly more effective than vehicle in improving central macular thickness in patients with DME.[178]

AG-73305 is a bi-specific (anti-VEGF and anti-integrin) Fc-fusion protein, currently enrolling in a phase II clinical trial for DME patients; preliminary results showed a dose-dependent improvement in best-corrected visual acuity and CST.[60]

As for the treatment of nAMD, a new promising strategy is represented by efdamrofusp alfa (IBI302), which is globally the first bispecific fusion protein that binds both the VEGF family, thereby inhibiting the neoangiogenic signaling pathway, and the C3b and C4b, reducing the complement-mediated inflammatory response. A prospective randomized, open-label, multiple ascending-dose, phase 1b study assessed the efficacy, safety, and tolerability of efdamrofusp alfa in patients with nAMD.[77] Among the 18 patients in the study, 6 received efdamrofusp alfa 2 mg, 6 received efdamrofusp alfa 4 mg, and 6 received aflibercept 2 mg. At week 20, mean changes from baseline in best-corrected visual acuity and anatomic outcomes were similar among the 3groups.[77]

The oral small molecule CCR3 inhibitor (AKST4290) inhibits the action of eotaxin, which may reduce the inflammation and neovascularization of nAMD.[41,82,180] In a prospective, multicenter, open-label phase IIa pilot clinical study, 30 patients with newly diagnosed nAMD received oral treatment with AKST4290 (400 mg) twice daily for 6 weeks.[180] The results of this study found a best-corrected visual acuity improvement of $+7.0 \pm 12.5$ letters at week-6, with 16 patients (55.2 %) experiencing a visual acuity gaining ≥ 5 letters. Regarding safety, all adverse events were mild or moderate in severity, and no additional safety issues were reported.[180]

Other new strategies for nAMD treatment not included in our review are based on subretinal or intravitreal gene therapy which may induce constitutive VEGF inhibition.[27,91]

6. Conclusion

We review the role of inflammation in nAMD and DME, its therapeutic relevance, and its unique implication in disease development. The concentration of specific aqueous humor cytokines indeed, seems to be disease dependent. In DME eyes the levels of proinflammatory cytokines/chemokines, IL-8 and MCP-1 are higher than in nAMD, and more importantly, IL-6 and ICAM-1 were exclusively found in the vitreous humor of eyes with DME.[86] Additionally, DME patients with higher levels of inflammatory markers, e.g., IL-8, IL-6, IL-1b, and ICAM-1 in the serum as well as in the aqueous humor, do not adequately respond to the anti-VEGF treatment.[3,72]

A further distinction to take into consideration is the cell groups involved in the development of such conditions. In DR/DME there is a dysfunction of a complex and multicellular structure, known as NVU, composed by endothelial cells, neurons, glia, smooth muscle cells, pericytes, and extracellular matrix.[102,106,119,130,137,155,159] This dysfunction has been associated with BRB breakdown and increased vascular leakage and cytokine release, which may lead to the development of DME.[61,96,102,103] Whereas, in nAMD the complex of choroid, photoreceptors, RPE, and Bruch membrane is the paramount of the disease development[16,38,115,158] leading to the initiation of different processes, including microglia activation, parainflammation, innate immune response, and complement activation.[16,36,38,53,66,76,78, 111,135,138,156,185].

Despite several inflammatory pathways that have been proven to be upregulated in both DME and nAMD, for now, it is not proven the therapeutical relevance of inflammation in nAMD where anti-VEGF still holds a major role. By contrast, in DME inflammation plays a pivotal role and is therefore a main therapeutic target.

Finally, inflammation and neoangiogenesis are, respectively, the hallmarks of DME and nAMD,[1 116,124,128,181,183,195,198,201]; the interplay among them clearly remarks how different those diseases are from each other and the need for a patient-personalized approach.

CRediT authorship contribution statement

Simone Donati: Writing – review & editing, Writing – original draft, Validation, Conceptualization. **Carlo Astarita:** Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Formal analysis, Conceptualization. **Valentina Gallinaro:** Writing – review & editing, Writing – original draft, Conceptualization. **Elisabetta Pilotto:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Data curation, Conceptualization. **Stela Vujosevic:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Conceptualization. **Marco Lupidi:** Writing – review & editing, Writing – original draft, Visualization, Data curation, Conceptualization.

Authors' contribution

All authors contributed to the preparation and critical review of the manuscript, and all of them approved the final manuscript.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: S. Vujosevic is a consultant for Abbvie, Boehringer and Ingelheim, Bayer, Novartis, Roche, Zeiss. C. Astarita and V. Gallinari are AbbVie employee and may own AbbVie stocks/options.

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