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Soluble Mediators of Diabetic Macular Edema: The Diagnostic Role of Aqueous VEGF and Cytokine Levels in Diabetic Macular Edema

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Abstract

Diabetic macular edema (DME) is a significant cause of vision loss and represents an important clinical and public health problem. It is characterized by breakdown of the blood retinal barrier with fluid accumulation in the sub-retinal and intra-retinal spaces. Although several hypotheses exist for the causes of diabetic macular edema, specific molecular mechanisms remain unclear. Current thinking includes the role of vascular endothelial growth factor (VEGF) and inflammatory cytokines in vascular permeability. We review studies showing a relationship between elevated aqueous VEGF, monocyte chemoattractant protein -1, interleukin 6, or interleukin 8 in association with DME and as predictors of DME. The presence of mediators in both the angiogenesis and inflammatory pathways data suggest a multifactorial model for the development of DME. Further studies targeting individual cytokine activity will be important to our understanding of the pathogenesis and treatment.

Keywords

Diabetes mellitus; macular edema; VEGF; diabetic retinopathy; cytokines

Introduction

Diabetes mellitus (DM) is a systemic condition that causes cumulative damage to tissues perfused by micro- and macro-vascular beds. In diabetic retinopathy (DR), initially, retinal neural and vascular injury set the stage for later disease manifestations that threaten visual acuity. DR is the leading cause of visual impairment and disability in the working age population within economically developed countries and, therefore, represents a significant health and economic burden (1). Diabetic macular edema (DME) is the most common cause of decreased vision in patients with DM and is present in approximately 20–30% of individuals with DM (2). The molecular pathophysiology of DME is still not well understood. Clinically, DME is characterized by accumulation and detection of extracellular fluid within and beneath layers of the retina. DME occurs, in part, because of loss of integrity of the blood retinal barriers and inability to handle the resulting extracellular fluid and compounds. Evidence supports a multifactorial pathophysiology for DME based on molecular changes that allow for these events to occur. Specifically, studies have

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demonstrated that loss of pericytes, thickening of basement membranes, advanced glycation end product (AGE) deposition, glial changes, and deterioration of the neurovascular unit are associated with and appear fundamental to the process of DME; however, the necessary and sufficient molecular mechanisms that allow DME to occur remain incompletely understood [3; 4]. For example, the ocular environment tends to maintain the structure of the retina intact and includes mechanisms to transport fluid from the subretinal space toward the choroid, but these innate functions are overwhelmed in DME. Due to the broad spectrum of molecular pathologies that may influence the development of DME, it is therapeutically challenging to treat. Thus, greater insight into the underlying pathophysiology is needed. Herein, we review the clinical evidence for evolving pathomechanisms and implications for development of novel therapies for DME.

Macular laser photocoagulation has long been a standard therapy for DME based on clinical trial evidence and long-term experience. The recommendations are based on data from the Early Treatment Diabetic Retinopathy Study (ETDRS) trial, which provided definitions for clinically significant macular edema (CSME) and guidelines for treatment with photocoagulation. This trial reported a 50% reduction in moderate loss of visual acuity due to macular edema at 3 years following macular photocoagulation and concluded that there was a benefit to performing focal photocoagulation in eyes with CSME [5]. The underlying mechanism by which macular laser improves DME is unclear. However, one theory is that ischemia in areas of capillary non-perfusion led to leaking walls of dilated capillaries and potentially dysfunction of the retinal pigment epithelium (RPE) to pump fluid from the retina to the choroid. In these areas, focal/grid laser treatment may improve oxygenation of the inner retina by eliminating oxygen dependent photoreceptors and facilitating the migration of neighboring healthy RPE into areas where laser was performed [6]. In areas of microaneurysms, photocoagulation is believed to cauterize the leaking vascular structures and prevent further fluid leakage into the sensory retina. Overall, however, the rationale for macular photocoagulation is largely based on an observational rather than on a mechanistic approach to DME. More recent insights into the underlying molecular mechanisms responsible for the development of DME have led to further advances in the therapy for DME. These include targeting inflammatory and angiogenic mediators. Interestingly, however, the individual patient response to therapy is variable, suggesting that there is a balance of etiologic factors that we as yet do not fully appreciate [7–8].

Vascular endothelial growth factor (VEGF) as a predictor and mediator of DME

Anti-VEGF intraocular therapy is emerging as a first-line therapy for the treatment of DME. The VEGF family, particularly the isoform VEGF-A, has been implicated in a number of ocular pathologies, including angiogenesis and DME. VEGF-A has been shown to be up-regulated in hypoxic tissue. In DR, loss of retinal capillaries is believed to lead to hypoxia, which is the stimulus for increased retinal expression of VEGF-A, mediated through hypoxia-inducible factors [9]. Aside from its angiogenic role, VEGF-A is also a known vascular permeability factor [9]. Thus, the role of VEGF in vasopermeability may be central to DME pathogenesis.

VEGF is soluble and, therefore, can be measured in fluid compartments within the eye as an indicator of increased retinal VEGF. A number of studies have been done that tested aqueous samples for VEGF levels as a means to predict risk of DME or postoperative CME. For example, the concentration of VEGF has been shown to be significantly elevated in both the vitreous fluid and the aqueous humor of patients with DME [10]. Furthermore, Funatsu et al., using a cross sectional study design of 54 eyes from patients with DM, found that the aqueous levels of VEGF are significantly correlated with the severity of macular edema as

assessed using biomicroscopy and fluorescein angiography [11]. As a predictive indicator, aqueous VEGF has been shown to be positively correlated with a clinically meaningful percent change in central subfield thickness as measured by optical coherence tomography at one month following cataract surgery in diabetic patients, suggesting that aqueous VEGF may have predictive value when determining postoperative macular thickening in diabetic patients undergoing cataract surgery [12].

The sentinel efficacy studies for anti-VEGF therapy, Ranibizumab for Edema of the macula in Diabetes-2 (READ-2) and Ranibizumab in Diabetic Macular Edema Study (RESOLVE) demonstrated that intravitreal ranibizumab was superior to either focal laser at 24 months or sham injection at 12 months and thus was an effective therapeutic strategy for management of DME [13–14]. These data were substantiated in the recent RISE and RIDE trials and DRCR.net Protocol I study which demonstrated improved visual acuity and macular anatomy in DME patients treated with ranibizumab when compared to sham [15–16]. These data suggest a primary role for anti-VEGF therapy in the treatment of DME. However, although VEGF is clearly an important mediator of DME, data support a multifactorial rather than singular etiology of DME. The multicenter study performed by the DRCR.net reported that visual outcomes were superior in anti-VEGF treated eyes as compared to steroid treated eyes, but in patients pseudophakic at baseline, results following anti-VEGF or steroid treatments were equivalent at one year [16]. Thus, independent treatment strategies achieved equivalent results with regard to anatomic and visual outcomes in the short-term in a subgroup of patients. A multifactorial pathology is further supported by the fact that only 40–50% of patients achieve “success” of VA of 20/20 or better or resolution of retinal thickening with anti-VEGF treatment [15–16]. In fact, Funk et al., demonstrated that treatment with bevacizumab decreased aqueous VEGF to sub-physiologic levels; however, there was not a linear correlation between the overall change in pre- and post-treatment VEGF levels with visual acuity based on changes in lines on the ETDRS chart or central retinal thickness based on change in microns as determined by Stratus optical coherence tomography (OCT) [17]. Furthermore, the investigators were unable to show that the pre-treatment level of aqueous VEGF was predictive of post-treatment anatomic response or visual outcome using the same outcome measures. The lack of correlation between aqueous VEGF levels and treatment effect may be related to study population, type of anti-VEGF therapy, dosing parameters, duration of DME and chronic effects on tissue, or indicate that aqueous VEGF is not an appropriate marker for retinal VEGF activity. However, the differences may also suggest that other upstream or parallel pathways of the VEGF signaling pathway may be important for development of DME and that VEGF alone is not the sole etiologic factor responsible for DME development.

Cytokines as predictors and mediators of DME

Other proposed mediators of DME include members of the inflammatory cascade. The role of inflammation in the pathogenesis of DME is hypothesized given its known role in vasopermeability, and more recently based on the efficacy of intravitreal steroid treatment of DME. Furthermore, the formation of advanced glycation end-products and oxidized low density lipoproteins, both of which are potentiated by elevated blood glucose levels, have been shown to lead to aberrant cell signaling causing activation of the innate immune system and attraction of monocytes [18]. Macrophage depletion studies in rodent models have shown that the presence of macrophages in the retina is necessary for the development of DR, and it is postulated, DME [19]. Early work linking inflammation with DME was reported and followed by the use of intravitreal steroid for treatment of DME or DME refractory to focal laser [19–20]. Several subsequent studies suggested superiority of both intravitreal steroid alone and intravitreal steroid combined with focal laser compared with focal laser alone [21–22]. However, investigation by the DRCR.net in 2008 demonstrated

equivalent visual and anatomic outcomes between patients treated with focal laser versus intravitreal steroid at 1 year; at year 2, focal laser appeared more efficacious [23]. Furthermore, visually significant cataract formation and elevated intraocular pressures were significantly associated with intravitreal steroid treatment in this study. Therefore, steroid therapy has some efficacy for treatment of DME; however, it also leads to development of visually significant side effects.

Cytokines are the classic mediators of inflammation and thus have been hypothesized to play a role in the development of DME. They represent a potential alternative, and more targeted strategy to address the inflammatory component of DME with fewer side effects than intraocular steroid treatments. As with VEGF, cytokines are soluble mediators and thus aqueous levels have also been proposed as surrogate markers for retinal cytokines.

Interleukin 6 (IL-6) is a cytokine that functions widely throughout the inflammatory cascade and is known to induce acute phase reactions and increase vascular permeability [24]. In a cohort of 54 individuals with DME, elevated aqueous IL-6 correlated with increased severity of DME as detected by leakage on fluorescein angiography and biomicroscopic evidence of CSME described in the ETDRS trial. [5; 25] Subsequent work by the same group demonstrated that elevated aqueous levels of IL-6 were associated with increased macular fluorescein leakage in diabetic patients 6 months following cataract surgery [26]. Recent work has confirmed these findings in a sample of 50 eyes, in which increased central subfoveal macular thickness measured by optical coherence tomography (OCT) was correlated with increased aqueous levels of IL-6 [27]. Interestingly, following treatment of DME with intravitreal bevacizumab, recurrence of DME was associated with elevated aqueous IL-6 but not VEGF, suggesting that recurrent macular edema may occur via an IL-6-mediated mechanism independent of VEGF [10]. However, another study, with much smaller numbers (N = 10) was unable to replicate the finding of increased aqueous IL-6 in patients with DME compared to age-matched controls without DM [17]. Notably, this study reported on data collected from mainly a Caucasian population, whereas the earlier described data were collected primarily from Asian populations, suggesting that differences between the studies could be related to ethnicity or underpowering due to smaller sample sizes.

Monocyte chemoattractant protein 1 (MCP-1) is a chemotactic chemokine that induces monocyte and macrophage infiltration into tissue. As a function of this role, MCP-1 has been implicated in leukostasis leading to retinal hypoxia in a rabbit model [28].

Furthermore, monocyte and macrophage recruitment to vessel walls has been shown to promote vascular permeability potentiating DME [18]. Initial studies demonstrated a statistically significant correlation between the levels of vitreous MCP-1 and the severity of DME [29]. Recent work has also shown a correlation between elevated aqueous MCP-1 and the presence of DME [17]. In a study by Sohn et al., aqueous MCP-1 was significantly elevated in patients with DME versus controls without DM and the elevated MCP-1 was significantly reduced following treatment with intravitreal steroid, in association with a reduction in overall central macular thickness [30].

Interleukin 8 (IL-8) is a pro-inflammatory and angiogenic cytokine produced by endothelial and glial cells in ischemic retina [31]. Classically, IL-8 is known as a neutrophil chemotactic factor and T-cell activator in the innate immune system. Aqueous levels of IL-8 have been shown to increase with progression of DR from mild NPDR to severe NPDR [27]. A number of studies have also demonstrated that IL-8 is significantly elevated in the aqueous fluid of diabetic patients with DME compared to diabetic patients without DME [10; 17]. Furthermore, these studies have demonstrated that following intravitreal anti-VEGF or

triamcinolone, aqueous IL-8 levels were unaffected [30]. Thus, the contribution of IL-8 to diabetic macular edema may represent an upstream, if not unique, immune pathophysiology. In support of this hypothesis, IL-8 has been shown to be positively correlated with severity of macular edema in the setting of DME but not macular edema resulting from branch retinal vein occlusion [32]. Thus, IL-8 appears to play a role in the development of DME, specifically, although IL-8 induced DME may not be adequately treated by current intravitreal anti-VEGF or steroid therapies and therefore could represent a new target for treatment of DME.

Conclusions

The underlying pathophysiology of DME and the molecular mediators involved are not well understood and, therefore, DME remains a clinical treatment dilemma. This may be partly due to our inability to adequately assess mechanism in human studies and the lack of adequate animal models. Current data suggest a role for VEGF and inflammatory cytokines. There is a great deal of overlap in pathways of VEGF and cytokines. For example, several members of the inflammatory cascade, such as toll-like receptor 3, IL-6, and MCP-1, have been implicated in the activation of VEGF suggesting a fundamental role for VEGF in the inflammatory response [33]. VEGF-A can up-regulate MCP-1 mRNA in cultured endothelial cells, and, in an *in vivo* angiogenesis model using a chick chorioallantoic membrane, MCP-1-induced angiogenesis was completely inhibited by a VEGF inhibitor [34]. Furthermore, IL-6 has been shown to promote angiogenesis specifically via induction of VEGF expression [24; 35]. Thus, data suggest that there may be interplay between these critical pathways leading to breakdown of the blood retinal barrier and subsequent DME. In this model, due to pathway overlap and crosstalk, the “final common pathway of DME” may be obtained through any number of combinations of molecular effectors. Thus targeting the process narrowly may not obtain the most efficacious result.

Alternatively, there may be an upstream necessary and sufficient molecular “switch” that if targeted would inhibit many mediators of DME. However, there are no studies targeting specific cytokine function in DME. It is clear from the data that targeting VEGF alone with currently available therapies does not lead to a consistent and permanent reduction in DME in all patients. It is interesting that the known cytokine that does not demonstrate a response to intravitreal steroid or anti-VEGF is IL-8. This suggests that our current therapies are not effectively reducing IL-8 function. IL-8 has been specifically targeted in other models of intraocular inflammation, for example in a rabbit model of endotoxin-induced uveitis using an intravitreally injected anti-IL-8 antibody. In this model, the presence of the anti-IL-8 antibody caused a decrease in the clinical and histologic grade of inflammation [36]. IL-8 is known to play a pivotal role in other ocular inflammatory conditions such as Behçet’s disease. In patients with Behçet’s disease, aqueous IL-8 levels have been shown to correlate positively and in a statistically significant manner with the severity of Behçet’s anterior uveitis as measured by the presence or absence of hypopyon [37].

More conclusive data are needed to determine if any one cytokine can be used to predict severity of DME or influence response to treatment with either intravitreal steroid or anti-VEGF agents. Additional pre-clinical studies may be considered to test the role of IL-8 as an upstream or unique mediator of DME. Current studies allude to a vast network of signaling pathways ultimately responsible for the development of DME, although mechanistic details of the signaling events remain unclear. However, it does appear that DME has a multifactorial etiology. A greater understanding of the molecular events required for its development may lead to more targeted therapies to be used solely or in conjunction with other treatments, and provide more effective and safer ways to treat DME.

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