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REVIEW ARTICLE

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Changes in aqueous and vitreous inflammatory cytokine levels in proliferative diabetic retinopathy: a systematic review and meta-analysis

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BACKGROUND: Diabetic retinopathy is a major complication of diabetes mellitus, where in its most advanced form ischemic changes lead to the development of retinal neovascularization, termed proliferative diabetic retinopathy (PDR). While the development of PDR is often associated with angiogenic and inflammatory cytokines, studies differ on which cytokines are implicated in disease pathogenesis and on the strength of these associations. We therefore conducted a systematic review and meta-analysis to quantitatively assess the existing body of data on intraocular cytokines as biomarkers in PDR.

METHODS: A comprehensive search of the literature without year limitation was conducted to January 18, 2021, which identified 341 studies assessing vitreous or aqueous cytokine levels in PDR, accounting for 10379 eyes with PDR and 6269 eyes from healthy controls. Effect sizes were calculated as standardized mean differences (SMD) of cytokine concentrations between PDR and control patients.

RESULTS: Concentrations (SMD, 95% confidence interval, and p-value) of aqueous IL-1β, IL-6, IL-8, MCP-1, TNF-α, and VEGF, and vitreous IL-2, IL-4, IL-6, IL-8, angiopoietin-2, eotaxin, erythropoietin, GM-CSF, GRO, HMGB-1, IFN-γ, IGF, IP-10, MCP-1, MIP-1, MMP-9, PDGF-AA, PlGF, sCD40L, SDF-1, sICAM-1, sVEGFR, TIMP, TNF-α, and VEGF were significantly higher in patients with PDR when compared to healthy nondiabetic controls. For all other cytokines no differences, failed sensitivity analyses or insufficient data were found.

CONCLUSIONS: This extensive list of cytokines speaks to the complexity of PDR pathogenesis, and informs future investigations into disease pathogenesis, prognosis, and management.

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INTRODUCTION

Proliferative diabetic retinopathy (PDR) represents the most advanced stage of diabetic retinopathy. PDR affects approximately 17 million people globally and is a leading cause of blindness among adults [1], making it a significant global health and economic problem. Characterized by neovascularization at the interface of perfused and non-perfused tissue, fragile new vessel formation and progressive fibrosis places patients with PDR at risk of severe visual compromise from vitreous haemorrhage, tractional retinal detachment, and neovascular glaucoma. While the pathophysiology of PDR is complex and not yet completely understood, it is known that microvascular ischemia, chronic inflammation, and retinal neurodegeneration are all important in the disease process [2].

As a result of prolonged hyperglycaemia, retinal blood vessels undergo pericyte and endothelial cell apoptosis [3, 4]. The resulting capillary occlusion and ischemia leads to upregulation of hypoxia-inducible factor 1 and angiogenic factors, the most studied of which is vascular endothelial growth factor (VEGF). VEGF contributes to the progression of PDR through increased vascular permeability and the promotion of endothelial cell proliferation [2]. The management of PDR with anti-VEGF therapy, therefore, has become increasingly common, although pan-retinal photocoagulation remains the mainstay of treatment. However, some patients may progress despite available therapies, including anti-VEGF agents and there remains a need for additional therapeutic targets and improved treatment algorithms.

The search for other intraocular cytokines that are involved in PDR pathogenesis has yielded a large body of literature. In addition to VEGF, angiogenic factors including insulin-like growth factor-I, basic fibroblast growth factor, platelet derived growth factor, placental growth factor, and angiopoietin have all been implicated in retinal neovascularization [5, 6]. However, there remains inconsistency between studies regarding which cytokines are associated with PDR and the magnitude of this association. Clarity on the role of cytokines in PDR will aid in predicting disease severity, progression, treatment response, and identifying novel therapeutic targets. We have therefore conducted a systematic review and meta-analysis on the association of intraocular

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cytokines and PDR to address these inconsistencies and to quantitatively summarize the literature.

METHODS

A detailed account of the methods used in this meta-analysis is available in our companion article on nonproliferative diabetic retinopathy (NPDR) in this issue, and is similar to those used in our previous work on a diabetic macular oedema [7]. In brief, a systematic literature search was done using Ovid MEDLINE, Embase, and Web of Science databases without year limitation until January 18, 2021. The search statements are available in Supplementary Fig. S1.

Studies were assessed by two independent reviewers using the following exclusion criteria: (1) the study did not examine a correlation, clinical outcome or response to treatment of an aqueous or vitreous cytokine; (2) was on subjects other than human adults; (3) included subjects with diabetic macular oedema; and (4) was a review article, editorial, or opinion piece. Studies that assessed the correlation of cytokines to clinical outcomes (prognostic biomarkers) or disease correlation to cytokine concentrations (diagnostic biomarkers) were evaluated for their risk of bias using the Quality in Prognosis Studies (QUIPS) tool or the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool, respectively [8, 9]. Modifications to QUIPS and QUADAS are provided in Supplementary Fig. S2.

Primary outcome measures were mean and standard deviation intraocular cytokine concentration and p-values for comparisons between those with PDR and non-diabetic participants, if a control group was available. Review Manager (Version 5.3.5, Nordic Cochrane Centre, Copenhagen, Denmark) was used to compute standardized mean difference (SMD) and 95% confidence interval for cytokine concentrations between patients with PDR and controls using the inverse variance method when there was sufficient data of at least three data points. The formulation of the SMD used was Hedges' adjusted g, selected as it includes an adjustment for small sample bias. A random-effects model was chosen because within-study and between-study variances were hypothesized to influence the true effect size. The magnitude of the SMD was defined as being very small if <0.20, small if 0.20-0.49, medium if 0.50–0.79, and large if ≥0.80. Between-study heterogeneity was assessed using the Cochrane Q test and I^2 statistic as described previously. Statistical difference for the Cochrane Q test was set as $p < 0.05$; I^2 statistics of 0.25, 0.50 and 0.75 denoted low, medium and high levels of heterogeneity, respectively, as per previous literature [10].

A sensitivity analysis was undertaken by removing one study at a time to assess outcome stability; if the effect size significantly changed with the removal of a single study, the data for that cytokine was deemed to have failed the sensitivity analysis. To determine if the results of this study were influenced by participants having previously received treatment for their PDR, two subgroup analyses were performed: one included only studies where patients had received no treatments for PDR within 3 months of sample collection; the other included only studies where all patients were treatment naïve.

RESULTS

The initial search identified 2947 records, of which 1681 remained after automated removal of duplicates. Following review at the full-text level to ensure that no cytokine concentrations were missed, 480 studies met the inclusion/exclusion criteria and 341 of those were specific for PDR (Fig. 1). These 341 studies encompassed for 10379 eyes with PDR and 6269 eyes from healthy controls [11–351].

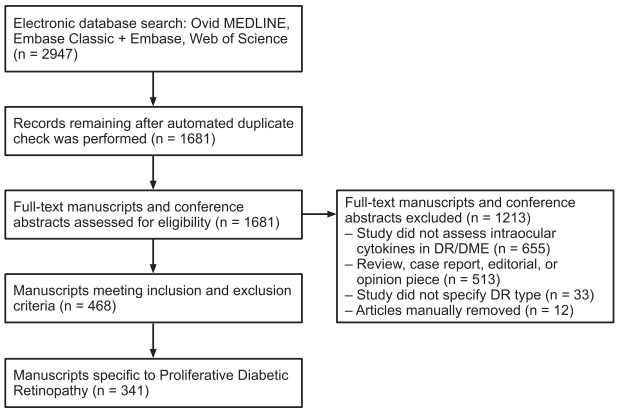

Fig. 1 Flow of information through the different phases of the systematic review; the initial search, duplicate removal, full-text elegibility, and manuscripts on proliferative diabetic retinopathy meeting inclusion criteria.

Study characteristics

Population and study characteristics are summarized in Table 1. Vitreous cytokines were assessed in 82% (279/341) of studies, with only 12% (41/341) assessing aqueous cytokines and the remaining 6% (21/341) assessing both vitreous and aqueous cytokines. Most studies (57%, 193/341) did not specify the type of diabetes in PDR patients, while 24% (81/341) of studies used participants with type 2 diabetes, 1% (3/341) of studies used those with type 1, and 14% (46/341) used patients with either type 1 or type 2 diabetes. The remaining studies classified patients by treatment status; 0.6% (2/341) were insulin dependent, 0.3% (1/341) were non-insulin dependent, and 4% (14/341) used both insulin dependent and independent patients. The analytical method used to quantify cytokine concentrations was clearly stated in 99% (340/341) studies, with the enzyme-linked immunosorbent assay and multiplex assay being most frequently used in 70% (239/341). Of the 293 studies with a control arm, the most commonly used control was eyes with epiretinal membrane or macular hole (38%, 111/293), with cataract surgery, retinal detachment, macular pucker, vitreous haemorrhage, vitreous floaters, vitreomacular traction, lens dislocation, and lens subluxation also being used as controls.

Quality assessment

Diagnostic biomarker studies. Two hundred and seventy-nine studies (82%) evaluated the diagnostic potential of intraocular cytokines and were assessed for quality using QUADAS (Fig. 2a), with further details available for individual studies in Supplemental Table S1. A case-control design was used in 88% (246/279) of studies and the selection criteria were clearly stated in 71% (198/279). There was a low risk of selection bias in 70% (195/279). Selected patients were an appropriate match for the study question in every case and all enrolled patients were included in the final analysis in 94% (263/279) of studies. The index text demonstrated a low risk of study bias in all studies, but was never interpreted without knowledge of the reference standard. All studies had each participant receiving the same reference standard, classified PDR appropriately and matched the review question, and in no studies was it interpreted independently from the index test (100%, 279/279). There was an overall low risk of bias in diagnostic studies.

Prognostic biomarker studies. Sixty-two studies (18%) evaluated the prognostic potential of cytokines. The overall QUIPS assessment is shown in Fig. 2b, and study details are available in Supplemental Table S2. There was a low risk of bias in study participation in 71% (44/62), and study attrition had a low risk of

Table 1. Population characteristics and intraocular markers investigated by the relevant studies identified in the systematic review.

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Abu El-Asrar et al. 1992	United States	Mean age 51, range 24-88, 61.5% male	IDDM	13	15	Cataract surgery	None	Vitreous	ELISA	IL-1, IL-6, IFN-γ, TNF-α
Aiello et al. 1994	United States	Investigated active and quiescent PDR, mean age 47, 46.3% male	Not specified	111	31	No neovascular disorders	None	Both	Radioimmunoassay (RIA)	VEGF
Kauffmann et al. 1994	United States	Excluded patients with previous vitrectomy, mean age 56.3 ± 3.9, 38.9% male	Not specified	18	11	Idiopathic macular pucker, VH, retinal tear, RD	None	Vitreous	ELISA	IL-1β, IL-6, IL-8, TNF-α
Adamis et al. 1995	Not specified	No patient details provided	Not specified	NA	NA	Non-PDR	None	Vitreous	Immunofluorometric assay	VEGF
Elner et al. 1995	Not specified	Pars plana vitrectomy for PDR who had either progressive fibrovascular proliferation and/or tractional retinal detachment or non-clearing vitreous hemorrhage	Not specified	30	26	Cadaveric	None	Vitreous	ELISA	IL-8, MCP-1, M-CSF
Esser et al. 1995	Germany	No patient details provided	T1DM, T2DM	NA	NA	Not specified	None	Vitreous	Sandwich enzyme immunoassay	sICAM-1
Abu El-Asrar et al. 1997	Saudi Arabia	Investigated a number of proliferative vitreoretinal disorders	Not specified	42	27	RD	None	Vitreous	Hybridoma growth activity	MCP-1, IL-6, IL-8
Ambati et al. 1997	United States	Selection criteria that patients had not undergone prior vitreous surgery or had a history of intraocular ischemia due to causes other than diabetic retinopathy, mean age 62.4 ± 23.1, 37.5% male	Not specified	22	28	Macular hole, ERM, CME, uveitis, endophthalmitis	None	Vitreous	ELISA	VEGF
Boulton et al. 1997	United Kingdom	Diabetic eyes had previously undergone laser photocoagulation, mean age 54.3	IDDM, NIDDM	51	21	Macular hole, RD	None	Vitreous	ELISA	bFGF, TGF-β2, IGF-I, IGFBP, EGF
Burgos et al. 1997	Spain	Both insulin and non-insulin dependent patients, mean age 52 ± 10.2	IDDM, NIDDM	20	13	ERM, subretinal membrane	None	Vitreous	ELISA	VEGF
Capeans et al. 1998	Spain	PDR eyes with vitreous hemorrhage, RD, or vitreoretinal membranes	T2DM	15	18	Cadaveric	None	Vitreous	ELISA	MCP-1, MIP-1α, MIP-1β
Elner et al. 1998	United States	No patients received preoperative periocular or systemic steroids, mean age 47	Not specified	30	10	Macular hole, macular pucker	None	Vitreous	ELISA	IL-8, IP-10
Katsura et al. 1998	Japan	Average HbA1c of 7.41 ± 1.7%, mean age 54.8 ± 8.5, 65.6% male	Not specified	73	17	Macular hole, preretinal membrane, RD	None	Vitreous	ELISA	VEGF, HGF
Khaliq et al. 1998	United Kingdom	No patient details provided	Not specified	NA	NA	Macular hole	PRP	Vitreous	NA	PlGF, VEGF
Barile et al. 1999	Not specified	All patients had a minimum follow-up interval of 12 months, mean age 51.9 ± 10.2, 72% male	Not specified	21	10	Macular hole	None	Vitreous	ELISA	sICAM-1, sVCAM-1
Deng et al. 1999	Not specified	No patient details provided	Not specified	27	14	Nondiabetic	None	Vitreous	ELISA	VEGF

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Hattenbach et al. 1999	Germany	Surgery for vitreoretinopathy or retinal detachment	Not specified	14	9	RD	None	Vitreous	ELISA	VEGF, PAI, UPA, TPA
Kosano et al. 1999	Japan	PDR classified as naked, active, and quiescent, mean age 54.4 ± 9.0, 65.6% male	NIDDM	73	25	Macular hole, vitreous hemorrhage, RD	None	Vitreous	ELISA	proMMP-9, VEGF
Limb et al. 1999	United Kingdom	All patients had undergone laser photocoagulation for treatment of PDR	IDDM, NIDDM	55	12	Cadaveric	None	Vitreous	ELISA	sICAM-1, sVCAM-1, sE-selectin
Shinoda et al. 1999	Japan	High risk PDR, patients were excluded if they had previous intraocular surgery, renal dysfunction, hepatic disorder, or malignancy, mean age 57.5 ± 12.4	Not specified	35	32	Nondiabetic	None	Aqueous	ELISA	HGF, VEGF
Freyberger et al. 2000	Germany	Four of the PDR patients had rubeosis iridis	Not specified	23	19	RD	None	Vitreous	ELISA	PDGF-AB
Mitamura et al. 2000	Japan	Excluded patients who had a history of vitreoretinal surgery before sampling, mean age 57.6, 46.6% male	Not specified	32	41	Macular hole, ERM	None	Vitreous	ELISA	MIF
Shinoda et al. 2000	Japan	Exclusion criteria of neovascularization of the iris or angle, prior intraocular surgery, ischemic cerebrovascular disorders, hepatic disfunction, malignancy, nephropathy resulting in hemodialysis, mean age 53.9 ± 13.1, 69.6% male	IDDM, NIDDM	46	0	No control	None	Aqueous	ELISA	HGF, VEGF
Spranger et al. 2000a	Germany	None of the patients had undergone ocular surgery or laser coagulation within 2 months, mean age 60 ± 13.7, 43.6% male	T1DM, T2DM	34	19	Nondiabetic	None	Vitreous	Radioimmunoassay (RIA)	IGF-I, IGF-II, IGF-BP3
Spranger et al. 2000b	Germany	Most PDR patients had previous laser photocoagulation, mean age 61.1 ± 18.7, 50% male	Not specified	34	18	Nondiabetic	PRP	Vitreous	ELISA	bFGF, VEGF
Endo et al. 2001	Japan	The minimum interval between laser treatment and acquisition of samples was three months, mean age 65 ± 7	T2DM	22	60	Macular hold, RD, cataract surgery	PRP	Aqueous	ELISA	VEGF
Hernandez et al. 2001	Spain	Excluded patients with prior vitreoretinal sampling or vitreous hemorrhage within 2 months, mean age 48 ± 10	T1DM, T2DM	20	20	RD, ERM	None	Vitreous	ELISA	VCAM-1, VEGF
Kojima et al. 2001	Japan	Patients who had previous vitrectomy or inflammatory diseases were excluded, mean age 51.5 ± 9.5, 65.4% male	T1DM, T2DM	30	10	Premacular fibrosis	None	Vitreous	ELISA	IL-6
Limb et al. 2001	United Kingdom	The known duration of diabetes was 18 months to 40 years (median, 18 years)	IDDM, NIDDM	29	9	Macular hole	None	Vitreous	ELISA	TNF-α, sTNF-RI, sTNF-RII

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Mitamura et al. 2001	Japan	Consecutive patients, excluded those with prior vitreoretinal surgery, mean age 50.8, 51.9% male	Not specified	52	36	Macular hole, ERM	None	Vitreous	ELISA	MCP-1
Sakamoto et al. 2001	Japan	Patients with quiescent (7) and active (9) PDR, mean age 51 ± 13, 33.3% male	Not specified	16	35	Cataract surgery	None	Aqueous	ELISA	TF
Spranger et al. 2001a	Germany	PDR patients with and without previous photocoagulation, 50% male	T1DM, T2DM	8	19	Nondiabetic	PRP	Vitreous	Radioimmunoassay (RIA)	IGF-I, IGF-II, IGF-BP3
Spranger et al. 2001b	Germany	PDR patients with and without previous photocoagulation, mean age 61 ± 12.2, 54.1% male	T1DM, T2DM	37	19	Nondiabetic	PRP	Vitreous	Western Blot	PEDF
Yuuki et al. 2001	Japan	No patient details provided	Not specified	47	21	Macular hole	None	Vitreous	ELISA	IL-6, IL-8, TNF-α
Funatsu et al. 2002	Japan	Exclusion criteria of treatment with an ACE inhibitor or an angiotensin II receptor antagonist, and previous ocular surgery or inflammation, included patient with prior PRP, mean age 60.7 ± 10.5, 54.5% male	Not specified	51	16	Macular hole, ERM	None	Vitreous	ELISA	Ang-2, VEGF
Hernandez et al. 2002	Spain	Excluded patients with previous vitreoretinal surgery, vitreous hemorrhage within 2 months, and cases where intravitreous hemoglobin was detectable, mean age 50 ± 15, 39.1% male	T1DM, T2DM	23	17	Macular hole, ERM, RD, edema	None	Vitreous	ELISA	NOx, VEGF
Hogeboom van Buggenum et al. 2002	Netherlands	Excluded patients with other ocular vascular diseases, investigating role of ACE inhibitors, mean age 58, 32.3% male	T1DM, T2DM	31	11	Idiopathic macular pucker, lens dislocation, RD	None	Vitreous	Immunoassay	VEGF
Jiang et al. 2002	China	Patients were excluded if previous history of vitreoretinal surgery, intravitreal injection of long-acting gas or silicone oil surgery, ocular diseases other than diabetic VH, intravitreal anti-VEGF within 3 months, ocular surgery within 6 months, uncontrolled hypertension, and a history of coagulopathy, mean age 53.5 ± 9.6, 66.7% male	Not specified	15	0	No control	Intravitreal conbercept	Vitreous	Not specified	Ang-2, Angiogenin, VEGF, bFGF, EGF, HGF, Leptin, PDGF, PIGF
Ogata et al. 2002	Japan	Samples from eyes obtained during a repeat vitrectomy were excluded, 21 with active PDR, mean age 59.0 ± 8.2, 53.8% male	Not specified	28	14	Macular hole	PRP	Vitreous	ELISA	PEDF, VEGF

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Simo et al. 2002	Spain	Patients with previous vitreoretinal surgery, vitreous hemorrhage within 2 months, or photocoagulation within 3 months were excluded, mean age 55 ± 14, 45.9% male	T1DM, T2DM	37	21	Macular hole, ERM, RD	None	Vitreous	ELISA	IGF-I, VEGF
Umeda et al. 2002	Japan	All samples were obtained during the first operation with those collected at the time of re-operation were excluded, mean age 52.9 ± 12, 55.6% male	Not specified	27	9	Macular hole	None	Vitreous	ELISA	VEGF, HGF
Boehm et al. 2003	Germany	Exclusion criteria were blood pressures >170/95 mmHg, HbA1c values > 9%, and current smoking, mean age 73.3, 41.7% male	T1DM, T2DM	12	13	Cataract surgery	None	Aqueous	Western Blot	VEGF, PEDF
Cicik et al. 2003	Turkey	Excluded patients who had previously undergone vitrectomy, underlying inflammatory disease, penetrating trauma or non-rhegmatogenous detachment, mean age 55.9 ± 11.5	Not specified	23	21	Cadaveric	None	Vitreous	ELISA	IL-8
Funatsu et al. 2003	Japan	Exclusion criteria were previous ocular surgery or ocular inflammation, and RD associated with a retinal tear, mean age 55.8 ± 8.4, 72.7% male	Not specified	44	0	No control	None	Vitreous	ELISA	Endostatin, VEGF
Nakamura et al. 2003	Japan	Most patients had vitreous hemorrhage and/or tractional RD, mean age 54.8 ± 12.1, 48.4% male	T2DM	62	50	Macular hole, ERM, RD	None	Vitreous	chemiluminescent enzyme immunoassay	IL-6, Pentosidine
Nicoletti et al. 2003	Italy	Almost all PDR patients had previous peripheral laser photocoagulation, excluded patients with inflammatory diseases, age range 40-71	Not specified	30	18	Macular pucker, macular hole	None	Vitreous	ELISA	VEGF, IL-8, TGF-β1
Ozaki et al. 2003	Japan	Photocoagulation in all PDR patients except one, active in 19 eyes and quiescent in 8 eyes, mean age 53.6 ± 10.3, 77.8% male	Not specified	27	16	Macular hole	None	Vitreous	Competitive enzyme immunoassay	Endostatin, HGF, VEGF
Duh et al. 2004	United States	No patient details provided	Not specified	32	24	Macular hole, ERM, vitreous floaters	None	Vitreous	ELISA	PEDF, VEGF
Funatsu et al. 2004	Japan	Exclusion criteria of ACE inhibitor ARB, ocular surgery or inflammation, RD associated with a retinal tear, and rubeosis iridis, mean age 62.4 ± 9.6, 57.4% male	Not specified	61	0	No control	None	Vitreous	ELISA	Ang-2, VEGF

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Inomata et al. 2004	Japan	Exclusion criteria of prior intraocular surgery, anemia and massive vitreous hemorrhage, mean age 56.4 ± 10.6, 41.7% male	Not specified	12	12	Macular hole	None	Vitreous	ELISA	VEGF
Itakura et al. 2004	Japan	No eyes had undergone a previous vitreous surgery, no iris rubeosis or NVG before vitrectomy, mean age 53.9 ± 7.4, 33.3% male	Not specified	17	8	Macular hole	PRP	Vitreous	ELISA	VEGF
Rollin et al. 2004	Spain	Excluded those with previous intraocular surgery, glaucoma, systemic hypertension, heart failure, renal failure, HbA1c higher than 10.5, prior tractional retinal detachment or vitreous hemorrhage, mean age 63.8	T1DM, T2DM	22	29	RD, macular hole, dislocated lens	None	Vitreous	Radioimmunoassay (RIA)	ANP
Tashimo et al. 2004	Japan	Excluded those with hyphema or a history of vitreoretinal surgery, mean age 60.5, 60% male	T1DM, T2DM	24	31	Cataract surgery	None	Aqueous	ELISA	MIF, MCP-1
Canataroglu et al. 2005	Turkey	Three of the PDR patients had Grade 0 disease, four had Grade 1, and seven were classified as Grade 2, mean age 56.1, 28.6% male	Not specified	14	15	Cadaveric	None	Vitreous	ELISA	IL-6, IL-8
Hernandez et al. 2005	Spain	Patients with previous vitreoretinal surgery, vitreous hemorrhage within 2 months, and photocoagulation within 3 months were excluded, mean age 68 ± 5, 40.9% male	T1DM, T2DM	22	16	Macular hole, ERM, RD	None	Vitreous	ELISA	IL-8, IL-10, MCP-1
Katsura et al. 2005	Japan	Vitreous and serum sampling	Not specified	59	16	Macular hole	None	Vitreous	ELISA	VEGF, EPO
Malik et al. 2005	United Kingdom	The duration of diabetes was significantly greater in patients with retinopathy ($p < 0.01$), but A1c was similar, mean age 60	T1DM	11	23	Nondiabetic	None	Vitreous	Indirect immunoassay	VEGF
Patel et al. 2005	United Kingdom	Previous argon panretinal photocoagulation with fibrovascular tractional/ rhegmatogenous retinal detachment, mean age 58	T2DM	10	5	Macular hole	None	Vitreous	luminescence immunoassay	Ang-1, Ang-2
Perrin et al. 2005	United Kingdom	Vitrectomy for complicated PDR, also measured isoform expression	T1DM, T2DM	13	18	Macular hole, RD	None	Vitreous	ELISA	VEGF-A, VEGF-B
Sydorova et al. 2005	Ukrainian	Patients with previous vitreoretinal surgery, vitreous hemorrhage and laser coagulation within a 3-month period were excluded, mean age 55 ± 12, 38.9% male	T1DM, T2DM	18	20	Penetrating injury	None	Vitreous	ELISA	VEGF

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Watanabe et al. 2005a	Japan	Active PDR in 71% of patients, mean age 60.8 ± 10.1, 53% male	Not specified	73	71	Macular hole, ERM, RD	None	Vitreous	ELISA	VEGF
Watanabe et al. 2005b	Japan	Active PDR in 73% of patients, mean age 59 ± 9.6, 46.3% male	Not specified	41	18	Macular hole, ERM	None	Vitreous	ELISA	Ang-2, VEGF
Yokoi et al. 2005	Japan	PDR patients with and without iris rubeosis, mean age 53 ± 12.6, 48.8% male	Not specified	45	28	Macular hole, ERM	None	Vitreous	ELISA	VEGF
Abu El-Asrar et al. 2006	Saudi Arabia	Active PDR in 37 patients and inactive PDR in 51 patients, analyzed vitreous humor and serum, mean age 49.3 ± 12.1, 72.7% male	IDDM, NIDDM	88	57	RD	None	Vitreous	ELISA	I-309, MCP-1, MIP-1α, MIP-1β, MCP-3, MCP-2, ENA-78, GCP-2, IP-10, I- TAC, SDF-1, CXCR3
Ishizaki et al. 2006	Japan	No patients had received ACE inhibitors, mean age 56 ± 14, 29.4% male	Not specified	35	10	Macular hole	None	Vitreous	ELISA	VEGF, MMP-9
Mocan et al. 2006	Turkey	Vitrectomy for vitreous hemorrhage with or without tractional retinal detachment, mean age 59 ± 10.8, 25% male	T2DM	8	8	RD, macular hole, intraocular foreign body, vitreous hemorrhage	None	Vitreous	ELISA	IL-6
Patel et al. 2006a	United Kingdom	Patients with coexistent retinal disease or those who had a complicated cataract procedure were excluded, mean age 62	T2DM	4	0	No control	None	Aqueous	ELISA	VEGF, HGF, IL-1β
Patel et al. 2006b	United Kingdom	Previous laser with panretinal photocoagulation, excluded those with posterior vitreous detachment, macular traction, and macular ischemia	T2DM	22	8	Macular hole	None	Both	ELISA	VEGF-A, HGF, TGF-β, MMP 9, sFlt-1R, PEDF
Simo et al. 2006	Spain	Patients with previous vitreoretinal surgery, vitreous hemorrhage within 2 months, or photocoagulation within 3 months were excluded, mean age 52 ± 13, 53.6% male	T1DM, T2DM	28	30	Macular hole, ERM	None	Vitreous	ELISA	HGF, VEGF
Abdel Rasol et al. 2007	Egypt	Patients with rubeosis iridis, with or without neovascular glaucoma, were excluded, mean age 54.5 ± 12.1, 80% male	Not specified	10	8	Macular hole	None	Vitreous	ELISA	Ang-2, VEGF
Banerjee et al. 2007	United Kingdom	No patient details provided	Not specified	10	8	ERM	None	Vitreous	Multiplex bead analysis	IL-6, IL-10, IL-12, IL-13, IL-15, IL-17, TNF, GM-CSF, G-CSF, IFN-γ, CCL2, CCL3, CCL4, CCL5, CCL11, CXCL8, VEGF, EGF, FGF
Cui et al. 2007	China	Sixteen also had neovascularization of the iris	Not specified	41	21	Macular hole	None	Both	ELISA	PEDF, VEGF

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Fosmark et al. 2007	Norway	Patients who had undergone vitrectomy within the last 6 months or who revealed vitreous samples of reddish color were excluded, mean age 67, 61% male	T2DM	16	29	Nondiabetic	None	Vitreous	ELISA	VEGF
Funatsu et al. 2007	Japan	Exclusion criteria of prior ocular surgery, ocular inflammation, retinal tear, rubeosis iridis or rubeotic glaucoma, mean age 63.6 ± 10.5, 63% male	Not specified	73	0	No control	None	Vitreous	ELISA	IL-6, VEGF
Kawashima et al. 2007	Japan	Only subjects who had a history of neither intraocular surgery nor ocular inflammation were enrolled, mean age 58 ± 12.8	Not specified	28	10	Macular hole, ERM	None	Vitreous	ELISA	sIL-6R, VEGF
Petrovic et al. 2007	Slovenia	Patients with previous vitrectomy, neovascularization of nondiabetic cause, vitreous hemorrhage <2 months prior, ocular inflammation, and photocoagulation in the preceding 3 months were excluded, mean age 65.3 ± 8.9	T2DM	71	17	Macular hole	None	Vitreous	cytometric bead array	IL-8
Takagi et al. 2007	Japan	No patient details provided	Not specified	73	71	Nondiabetic	None	Vitreous	ELISA	EPO, VEGF
Adamiec-Mroczek et al. 2008	Poland	Laser photocoagulation was performed at an earlier stage of disease in all patients, mean age 64.83 ± 8.38, 36.8% male	T2DM	19	15	RD, Macular hole, macular pucker, lens dislocation	None	Vitreous	ELISA	ICAM-1, sVCAM-1, IL-6, TNF-α
Kakehashi et al. 2008	Japan	Mean age 55.9	Not specified	19	11	Macular hole, preretinal membrane, RD	None	Both	ELISA	VEGF, AGE
Kuiper et al. 2008	Netherlands	PDR inactive in 2, active in 19, and quiescent in 11, mean age 54.2 ± 12.7, 46.9% male	T1DM, T2DM	32	36	Macular pucker, macular hole	None	Vitreous	ELISA	CTGF, VEGF
Liinamaa et al. 2008	Finland	Overall, poorly controlled diabetes and hypertension, mean age 57.3 ± 13.8, 50% male	Not specified	53	42	Macular pucker, macular hole, vitreous hemorrhage, vitreous opacities, RD, intraocular lens subluxation	None	Vitreous	Chemiluminescent enzyme immunoassay	VEGF
Matsunaga et al. 2008	Japan	No patients with had prior intravitreal anti-VEGF injection or vitrectomy, mean age 59 ± 1.6, 42.3% male	Not specified	27	12	Macular hole	None	Vitreous	ELISA	sVEGFR-1, VEGF, PEDF
Merlak et al. 2008	Croatia	Excluded those with systemic inflammatory disease, mean age 65.33, 75% male	T1DM, T2DM	36	10	Not specified	None	Vitreous	ELISA	VEGF, VEGFR1, VEGFR2

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Murugeswari et al. 2008	India	Patients with other forms of retinopathy and other systemic infective/ autoimmune/other inflammatory disease were excluded, mean age 54.9 ± 8.9, 84% male	T2DM	25	25	Macular hole	None	Vitreous	ELISA	IL-6, IL-8, IL-1β, MCP-1, VEGF, PEDF
Patel et al. 2008	United Kingdom	Consecutive patients, most PDR patients had inactive fibrovascular membranes, mean age 58	T2DM	5	5	Macular hole	None	Vitreous	ELISA	ET-1, IL-1β, IL-1ra
Sawada et al. 2008	Japan	Bilateral PDR, bevacizumab used as adjunctive therapy, mean age 50, 80% male	Not specified	10	0	No control	Intravitreal bevacizumab	Aqueous	ELISA	VEGF
Adamiec-Mroczek et al. 2009	Poland	All patients on intensive diabetes therapy, excluded renal failure, liver damage, and cancer, mean age 64.63 ± 8.38, 36.8% male	T2DM	19	15	RD, Macular hole, macular pucker, lens dislocation	None	Vitreous	ELISA	ICAM-1, VCAM-1, E-selectin
Arimura et al. 2009	Japan	Eyes with massive vitreous hemorrhage or apparent tractional retinal detachment were excluded, mean age 62, 44.4% male	T2DM	18	0	No control	Intravitreal triamcinolone acetonide (TA) or bevacizumab	Vitreous	Bead-based multiplex immunoassay	Interleukin-1β, IL-6, IL-8, IL-10, IL-12p70, and TNF-α, SDF-1α, VEGF
Izuta et al. 2009	Japan	Samples with repeat vitrectomy were excluded, mean age 52.9 ± 10.6, 41.7% male	Not specified	14	14	Macular hole	None	Vitreous	ELISA	VEGF
Kinnunen et al. 2009	Finland	All patients had had panretinal laser photocoagulation, excluded previous vitreoretinal surgery, opening of the posterior lens capsule, and vitreous hemorrhage < 1 month old, mean age 60.41 ± 8.43	T1DM, T2DM	30	5	Macular hole	None	Vitreous	ELISA	VEGF-A, VEGF-C, VEGF-D, Ang-1, Ang-2, PlGF, PDGF-B, TIE-1, TIE-2, HIF-1α, VEGFR-1, VEGFR-2, VEGFR-3, NFkB
Matsuyama et al. 2009	Japan	Patients had neovascular glaucoma, rubeosis of the iris or angle structures, including trabecular meshwork with PDR, or aggressive PDR, mean age 59.7 ± 10.2, 80% male	T2DM	11	0	No control	Intravitreal bevacizumab	Aqueous	ELISA	VEGF, PEDF
Nakamura et al. 2009	Japan	Measured cytokines in a subset of PDR patients for comparison with VEGF genotypes SNP-634 and SNP-2578	T2DM	40	0	No control	None	Vitreous	ELISA	VEGF
Nam et al. 2009	South Korea	Also investigated proliferative vitreoretinopathy, mean age 54.9 ± 9.0	Not specified	8	0	No control	None	Vitreous	ELISA	VEGF, PEDF, PDGF, TGF-β1

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Praidou et al. 2009	Greece	Exclusion criteria included ocular surgery within 2 years, ocular inflammation, rubeosis iridis or neovascular glaucoma, and RRD, mean age 68.7 ± 7.8, 41.9% male	Not specified	33	18	Macular hole, ERM	None	Vitreous	ELISA	PDGF-AA, PDGF-AB, PDGF-BB, VEGF
Reverter et al. 2009	Spain	Patients with active or recent vitreous hemorrhage, previous ocular surgery, inflammatory ocular disease or trauma were excluded, mean age 57 ± 8, 100% male	T2DM	8	8	Macular hole	None	Vitreous	Array Analysis	ENA-78, GCSF, GM-SCF, GRO-α, I-309, IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p40, IL-12p70, IL-13, IL-15, IFN-γ, MCP-1, MCP-2, MCP-3, MCSF, MDC, MIG-γ, MIP-1γ, RANTES, SCF, SDF-1, TARC, TGF-β1, TNF-α, TNF-β, EGF, IGF-1, angiogenin, oncostatin M, thrombopoietin, PEDF-BB, VEGF
Shimura et al. 2009	Japan	Patients with renal dysfunction or poor glycemic control (HbA1c > 9.0%) were excluded, mean age 64.4 ± 5.9, 57.1% male	T2DM	14	0	No control	PRP	Vitreous	ELISA	VEGF, IL-6, SDF-1, RANTES
Wang et al. 2009	China	Patients with previous vitreoretinal surgery, vitreous hemorrhage <2 months prior, and photocoagulation <3 months prior were excluded, mean age 57 ± 15, 47.8% male	T1DM, T2DM	42	23	Macular hole, ERM, RD	None	Vitreous	ELISA	HIF-1α, VEGF
Yoshimura et al. 2009	Japan	Samples with obvious bleeding were excluded, mean age 55.8 ± 12.5, 70.7% male	Not specified	147	83	Macular hole, ERM	None	Vitreous	Bead-based multiplex immunoassay	IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-17, IFN-γ, TNF-α, IL-8, Eotaxin, MCP-1, MIP-1α, MIP-1β, RANTES, EGF, VEGF, bFGF, G-CSF, GM-CSF
Adamiec-Mroczek et al. 2010	Poland	Patients overweight, with concomitant hypertension, hypercholesterolemia, and hypertriglyceridemia, mean age 64.63 ± 8.38, 36.8% male	T2DM, IDDM	19	15	RD, Macular hole, macular pucker, lens dislocation	None	Vitreous	ELISA	ET-1, TNF-α, IL-6, sE-selectin
Chen et al. 2010	China	None of the patients had vitrectomy for any retinal disorders before	Not specified	41	12	Macular hole	PRP	Vitreous	ELISA	SDF-1, VEGF
Forooghian et al. 2010	Canada	Exclusion criteria included VH secondary to ocular disease other than diabetes, bevacizumab within the past 3 months, and triamcinolone during the past 6 months, mean age 47 ± 14, 69% male	T1DM, T2DM	29	0	No control	Intravitreal bevacizumab	Aqueous	ELISA	Ang-2, leptin, IL-1β, IL-2, IL-6, IL-8, IL-10, PDGF-AA, PDGF-AB, PDGF-BB, MCP-1, IFN-γ, TGF-β1, TGF-β2, VEGF, PlGF, PEDF, bFGF, TNF-α, ICAM-1

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Gustavsson et al. 2010	Sweden	No patient details provided	Not specified	NA	NA	Cataract surgery	None	Both	multiplex bead assay	IL-1β, IL-6, IL-8, TNF-α, GM-CSF, MCP-1, RANTES, bFGF, VEGF
Hattori et al. 2010	Japan	Compared patients with and without preoperative bevacizumab injection, mean age 60.1 ± 8.5	Not specified	40	0	No control	Intravitreal bevacizumab	Vitreous	ELISA	VEGF
Hernandez et al. 2010	Spain	Exclusion criteria of photocoagulation in the preceding 3 months or previous vitreoretinal surgery, vitreous hemorrhage within 3 months, intravitreous hemoglobin, and renal failure, mean age 60.6 ± 14.3, 42.1% male	T2DM	19	16	Macular hole	None	Vitreous	ELISA	LBS, sCD14, IL-8, MCP-1
Izuta et al. 2010	Japan	Samples with repeat vitrectomy were excluded, mean age 54.1 ± 13.6, 47.6% male	Not specified	21	21	Macular hole	None	Vitreous	ELISA	VEGF
Kobayashi et al. 2010	Japan	Eyes with and without anterior hyaloidal fibrovascular proliferation, mean age 43.2 ± 12.9, 81.8% male	Not specified	25	0	No control	None	Vitreous	ELISA	VEGF
Oh et al. 2010	South Korea	Exclusion criteria of previous intraocular surgery or injection and macular focal/grid laser photocoagulation within 3 months	Not specified	13	12	Cataract surgery	PRP	Aqueous	Bead-based multiplex immunoassay	IL-1β, IL-6, IL-8, TNF-α, MCP-1, IP-10, VEGF
Petrovic et al. 2010	Slovenia	Excluded patients with previous vitrectomy, nondiabetic neovascularization, vitreous hemorrhage <2 months prior, ocular inflammation, and photocoagulation within 3 months, mean age 64.6 ± 8.2, 55.6% male	T2DM	63	0	No control	PRP	Vitreous	cytometric bead array	IL-8, VEGF
Ponnalagu et al. 2010	India	No patient details provided	Not specified	9	5	Macular hole	None	Vitreous	Cytokine Biochip Array	IL-6, MCP-1, VEGF
Schwartzman et al. 2010	Italy	All patients with PDR had active disease, mean age 63 ± 3	T1DM, T2DM	13	9	ERM	None	Vitreous	Chemokine array	GRO-α, IL-8, IP-10, MCP-1, RANTES, TARC, Ang-2, bFGF, HGF, PDGF-BB, TIMP-1, TIMP-2, TNF-α, VEGF, TNFR-2, VEGFR-1, VEGFR-2
Selim et al. 2010	Turkey	Exclusion criteria of previous intraocular surgery or laser photocoagulation within 6 months, glaucoma or rubeosis iridis, previous vitrectomy or intravitreal injection of steroid or an anti-VEGF agent, mean age 65.1 ± 9.9, 44.4% male	Not specified	19	18	Cataract surgery	None	Aqueous	ELISA	VEGF

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Tao et al. 2010	China	Consecutive patients, mean age 52.2 ± 9.8, 51% male	T2DM	55	34	Macular hole, ERM	None	Vitreous	ELISA	Apelin, VEGF
Abu El-Asrar et al. 2011	Saudi Arabia	Active PDR was present in 15 patients, and inactive PDR was present in 14 patients, mean age 46.9 ± 9.9, 82.8% male	NIDDM, IDDM	29	17	RD	None	Vitreous	ELISA	sRAGE, GM-CSF, IL-1β, MCP-1, sICAM-1, HMGB-1
Arjamaa et al. 2011	Finland	Most samples were retinopathy class 3, mean age 48 ± 17, 48% male	Not specified	25	0	No control	None	Vitreous	ELISA	IL-6, IL-8
Asato et al. 2011	Japan	PDR was classified clinically as active if there were perfused, multi-branching iridic or pre-retinal neovascular capillaries, mean age 55.8 ± 1.9, 52.9% male	Not specified	51	30	Macular hole	None	Vitreous	ELISA	sVEGFR-1
De La Cadena et al. 2011	United States	No patient details provided	T2DM	11	5	Nondiabetic	None	Vitreous	ELISA	Thrombospondin-1, CTGF, TGF-β
Lange et al. 2011	United Kingdom	All patients phakic, excluded if previous intraocular surgery or intraocular hemorrhage or inflammation, mean age 52.2 ± 13.6	T1DM, T2DM	14	14	Macular hole, ERM	None	Vitreous	Multiplex array assay	EGF, Eotaxin, bFGF, Flt-3L, G-CSF, GM-CSF, GRO, IFN-α2, IFN-γ, IL-1α, IL-1β, IL-1ra, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12p40, IL-12p70, IL-13, IL-15, IL-17, IP-10, MCP-1, MCP-3, MDC, MIP-1α, MIP-1β, PDGF-AA, PDGF-AB, sCD40L, sIL-2ra, RANTES, TGF-α, TNF-α, TNF-β, VEGF
Liu et al. 2011	China	No patient details provided	Not specified	10	8	Macular hole, ERM, RD	None	Vitreous	ELISA	Netrin-1, VEGF
Ma et al. 2011	China	Exclusion criteria included treatment with corticosteroids or immunosuppressive agents, ocular surgery, uveitis, iris rubeosis, immune diseases, mean age 53.3 ± 12.1, 45% male	Not specified	76	31	Macular hole, ERM	None	Vitreous	ELISA	IL-6
Marek et al. 2011	Poland	Exclusion criteria included chronic disease (other than diabetes), neoplasm, previous vitrectomy, photocoagulation and intravitreal hemorrhages within 3 months, mean age 54.93 ± 6.67, 40% male	T1DM	10	15	RD, ERM	None	Vitreous	ELISA	Angiogenin, VEGF
Matsuyama et al. 2011	Japan	Patients with "aggressive" PDR were studied, mean age 59.8 ± 8.7, 50% male	T2DM	8	0	No control	Intravitreal bevacizumab	Aqueous	ELISA	VEGF
Nakamura et al. 2011	Japan	Samples with bleeding were excluded, mean age 56.1 ± 11.6, 51.4% male	Not specified	37	60	Macular hole, ERM	None	Vitreous	ELISA	Tissue Kallikrein, VEGF

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Praidou et al. 2011	Greece	Exclusion criteria included ocular surgery within 2 years, ocular inflammation, rubeosis iridis or neovascular glaucoma, and RRD, mean age 68.7 ± 7.8, 41.9% male	Not specified	33	18	Macular hole	None	Vitreous	ELISA	PDGF-AA, PDGF-AB, PDGF-BB, VEGF
Qian et al. 2011	China	Groups with and without preoperative bevacizumab, mean age 56 ± 7.4, 46% male	T2DM	24	0	No control	Intravitreal bevacizumab	Vitreous	ELISA	Apelin, VEGF
Reverter et al. 2011	Spain	Patients with active or recent vitreous hemorrhage, previous ocular surgery, inflammatory ocular disease or trauma were excluded, mean age 64 ± 14, 50% male	T2DM	12	12	Nondiabetic	None	Vitreous	Western Blot	IL-1α, IL-1β, IL-2, IL-7
Yoshida et al. 2011	Japan	Exclusion criteria were age >80 years, renal or hematologic disease, uremia, previous chemotherapy, and chronic disease other than diabetes, mean age 54.6 ± 8.7, 60.7% male	Not specified	106	31	Macular hole, ERM	None	Vitreous	ELISA	bFGF, VEGF, Periostin
Zheng et al. 2011	China	Samples from eyes obtained during a repeat vitrectomy were excluded, and no patients had prior surgery, mean age 56 ± 8.5, 37.5% male	T2DM	21	16	Macular hole	None	Vitreous	ELISA	Ficolin-3, VEGF, PEDF
Abu El-Asrar et al. 2012	Saudi Arabia	Active PDR in 19 patients and inactive PDR in 17 patients	Not specified	36	21	RD	None	Vitreous	ELISA	VE-Cadherin, VEGF, Eng, G-CSF, HMGB1
Baharivand et al. 2012	Iran	Vitrectomy for long-term vitreous hemorrhage and/or tractional retinal detachment, mean age 56 ± 10, 63.3% male	T1DM, T2DM	30	0	Nondiabetic	None	Vitreous	ELISA	VEGF
Citirik et al. 2012	Turkey	All patients were Turkish Caucasians, excluded those on systemic anti-inflammatory medication, history of ocular inflammation, previous intraocular surgery, prior intravitreal drug injection, mean age 55.79 ± 4.9, 64.3% male	Not specified	32	10	Traumatic lens dislocation	None	Vitreous	ELISA	VEGF
Huber et al. 2012	Germany	Patients with active PDR, mean age 67 ± 10, 50% male	Not specified	6	11	Macular hole, ERM	None	Vitreous	ELISA	PEDF, Ang-2, VEGF, sVEGFR-1

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Jeon et al. 2012	South Korea	Exclusion criteria of any pharmacologic intervention on the study eye within 6 months or fellow eye within 3 months, PRP within 3 months, prior PPV, myocardial infarction or stroke, mean age 55.83 ± 10.67, 60% male	T2DM	30	0	No control	Intravitreal bevacizumab	Aqueous	Suspension bead array	IL-2, IL-6, IL-8, TNF-α, TGF-β2, VEGF
Kanda et al. 2012	Japan	Pars plana vitrectomy for prolonged vitreous hemorrhage and tractional retinal detachment involving the macula, mean age 60.3 ± 7.7, 56.5% male	Not specified	23	16	Macular hole, ERM	None	Vitreous	ELISA	VEGF, sPRR
Katome et al. 2012	Japan	No patient details provided	T2DM	34	38	ERM	None	Both	ELISA	VEGF
Ma et al. 2012	China	Patients with and without preoperative IVB, exclusion criteria included systemic and previous treatment with anti-VEGF therapy, and previous ocular surgery or tumor, mean age 55.3 ± 8, 48% male	Not specified	27	13	Nondiabetic	Intravitreal bevacizumab	Vitreous	ELISA	VEGF
Matsumoto et al. 2012	Japan	Quiescent and active PDR, with a younger age in the latter, mean age 64.8 ± 11.2, 66.7% male	T2DM	43	21	ERM	Intravitreal bevacizumab	Vitreous	ELISA	VEGF, EPO
Mohan et al. 2012	India	Exclusion criteria of previous ocular surgery or inflammation, intravitreal therapy, macular edema systemic inflammatory diseases, mean age 58 ± 7.5, 44.6% male	T2DM	56	49	Macular hole, RD	None	Vitreous	ELISA	VEGF, EPO, PEDF
Murata et al. 2012	Japan	Vitrectomy for prolonged vitreous hemorrhage and tractional retinal detachment of macular lesions, mean age 58.8 ± 8.5, 59.5% male	Not specified	37	14	Macular hole, ERM	None	Vitreous	ELISA	sVAP-1
Schoenberger et al. 2012	United States	Exclusion criteria of previous vitrectomy, prior intravitreal injection within 3 months, history of ocular trauma, aphakia, presence of an anterior chamber intraocular lens, and enrollment of the fellow eye, mean age 56.1 ± 10.2	Not specified	13	13	Macular hole, ERM, vitreous opacity, dislocated IOL	PRP	Vitreous	Bead-based multiplex immunoassay	Eotaxin, Flt-3L, GRO, IFN-γ, IL-1β, IL-6, IL-8, IL-10, IL-12p40, IP-10, MCP-1, TNF-α, VEGF, RANTES, PDGF-AA, PDGF-AB
Sohn et al. 2012	United States	Exclusion criteria consisted of a history of PPV, dense vitreous hemorrhage, a history of stroke, thromboembolic event, or heart attack within 6 months, and pregnancy, mean age 50.3 ± 9.3, 63.2% male	Not specified	10	0	No control	Intravitreal bevacizumab	Both	ELISA	CTGF, VEGF

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Van Geest et al. 2012	Netherlands	Exclusion criteria were significant ocular co-morbidity, previous vitrectomy, and ocular surgery within 3 months of vitrectomy, mean age 53.2 ± 14.2, 61.5% male	T1DM, T2DM	52	0	No control	Intravitreal bevacizumab	Vitreous	ELISA	CTGF, VEGF
Wakabayashi et al. 2012	Japan	Exclusion criteria of prior vitreoretinal surgery except laser photocoagulation to treat PDR, prior intravitreal anti-VEGF antibody injection, iris and angle neovascularization, posterior capsule rupture during cataract surgery, intraoperative use of silicone oil, and <6 months of follow-up, mean age 58, 69.2% men	T1DM, T2DM	60	0	No control	None	Both	Cytometric bead array flex immunoassay	VEGF
Yoshida et al. 2012	Japan	Criteria for exclusion were previous intraocular surgery or ocular inflammation, retinal detachment associated with a retinal tear, age >80 years, renal and hematologic diseases, uremia, prior chemotherapy, and presence of chronic pathologies other than diabetes, mean age 56.9 ± 9.6, 66.7% male	Not specified	38	44	Macular hole, ERM	PPV	Vitreous	ELISA	VEGF, Endostatin
Zhou et al. 2012	China	Patients excluded if they had renal insufficiency, liver damage, or cancer, mean age 62.8 ± 9.0, 48.4% male	T2DM	62	20	Macular hole, RD	None	Vitreous	ELISA	IL-1β, IL-6, IL-8, IL-10, MCP-1, Endothelin-1, VEGF, TNF
Abu El-Asrar et al. 2013a	Saudi Arabia	Active PDR in 20 patients and inactive PDR in 22 patients, mean age 54.9 ± 13.6, 78.6% male	IDDM, NIDDM	30	22	RD	None	Vitreous	ELISA	ATX, VEGF
Abu El-Asrar et al. 2013b	Belgium	Vitrectomy for traction retinal detachment, combined traction/ rhegmatogenous retinal detachment, or vitreous hemorrhage	Not specified	32	24	RD	None	Vitreous	ELISA	MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-13, VEGF
Abu El-Asrar et al. 2013c	Saudi Arabia	Active PDR in 21 patients and inactive PDR in 13 patients, mean age 53.3 ± 11.7, 70.6% male	IDDM, NIDDM	34	15	RD	None	Vitreous	ELISA	VEGF, sVEGFR-2, SCF, s-Kit, eNOS
Abu El-Asrar et al. 2013d	Saudi Arabia	Active PDR in 16 patients and inactive PDR in 14 patients, interval between PRP and vitrectomy was 10.1 ± 5.7 months	Not specified	30	25	RD	None	Vitreous	ELISA	VEGF, VEGF-R1, TSP-1, TSP-2

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Bromberg-White et al. 2013	United States	No anti-VEGF therapy prior to vitrectomy but some PRP, mean age 58 ± 11, 51.1% male	Not specified	43	29	Macular hole, macular pucker, ERM	None	Vitreous	Bead-based multiplex immunoassay	sCD40L, Eotaxin, bFGF, FLT3L, GM-CSF, GRO, IFN-α2, IL-1α, IL-6, IL-7, IL-8, IL-10, IP-10, IL-12p40, MCP-1, MCP-3, MDC, MIP-1β, VEGF
Byon et al. 2013	South Korea	Groups with and without angiotensin receptor blockers, no intravitreal injections, mean age 52.4 ± 17.8, 37% male	T2DM	46	30	Macular hole, ERM	None	Vitreous	ELISA	VEGF
Dallinga et al. 2013	Netherlands	No patient details provided	Not specified	52	0	No control	None	Vitreous	ELISA	CEGF, VEGF
Gustavsson et al. 2013	Sweden	Included patients with history of hypertension, cardiovascular disease, and smoking, mean age 55, 57.7% male	T1DM, T2DM	26	27	Cataract surgery	None	Vitreous	Chemiluminescent enzyme immunoassay	IL-1β, IL-6, TNF-α
Hines et al. 2013	United States	No patient details provided	Not specified	12	0	No control	None	Vitreous	Reverse Phase Protein Microarray (RPPM)	VEGF-A, VEGFR-2, MMP-9, MMP-14
Igbre et al. 2013	United States	No patient details provided	Not specified	96	24	Nondiabetic	None	Vitreous	Reverse Phase Protein Microarray (RPPM)	MMP-9
Koskela et al. 2013	Finland	Diabetic patients with prior vitrectomy or intravitreal bevacizumab were excluded, mean age 59.4 ± 14.3, 40.7% male	T1DM, T2DM	39	16	Macular hole, ERM	None	Vitreous	Multiplex array assay	sE-selectin, sICAM-1, sICAM-3, sPECAM-1, sP-selectin, sVCAM-1, IL-1 β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10 IL-12p70, TNF-α, TNF-β, IFN-γ
Kuzmin et al. 2013	Russia	Patients >16 years old, excluded if previous vitreous, retinal or glaucoma surgery, eye infections, chronic or immune uveitis, systemic immune-suppressing therapy, mean age 68	T1DM, T2DM	27	27	Cataract surgery	None	Aqueous	ELISA	VEGF-A
Loukovaara et al. 2013	Finland	Preoperative injections of VEGF inhibitors were not given to the enrolled diabetic study eyes, mean age 51.5 ± 17.8, 53.6% male	T1DM, T2DM	51	40	Macular pucker, macular hole	PRP	Vitreous	ELISA	MMP-2, MMP-9, Ang-1, Ang-2, TNF-β, EPO, VEGF
Muramatsu et al. 2013	Japan	Vitrectomy for vitreous hemorrhage, traction retinal detachment, or macular edema, mean age 57.9 ± 8.7, 63.6% male	T2DM	12	11	Macular hole, ERM	None	Vitreous	Cytometric bead array flex immunoassay	VEGF, MCP-1
Nawaz et al. 2013	Saudi Arabia	Active PDR in 20 patients and inactive in the remaining 20 patients, vitrectomy for tractional RD and/or non-clearing vitreous hemorrhage	Not specified	40	29	RD	None	Vitreous	ELISA	VEGF, MCP-1, MIG, IP-10, PF-4
Nishiguchi et al. 2013	Japan	Consecutive patients, all with prior laser panphotocoagulation, mean age 40.3 ± 9.0	Not specified	7	15	Cataract surgery	None	Aqueous	ELISA	VEGF

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Parveen et al. 2013	Pakistan	Exclusion criteria were severe systemic illness, cardiac, renal or cerebral dysfunction, cataract, conjunctivitis, glaucoma and previous laser therapy, mean age 50.4 ± 6.6	T2DM	26	40	Nondiabetic	None	Vitreous	ELISA	IL-6, VEGF
Raiser et al. 2013	Turkey	High risk PDR patients, excluded those with ocular inflammation and laser within the past 3 months, mean age 65.9 ± 6.2, 59.7% male	T2DM	57	22	Macular hole	None	Vitreous	ELISA	IL-8, TNF-α
Tsubota et al. 2013	Japan	No patient details provided	Not specified	28	0	No control	Intravitreal bevacizumab	Vitreous	ELISA	VEGF
Van Geest et al. 2013	Netherlands	75% of patient with active neovascularization, mean age 58.6 ± 12.3, 53.6% male	T1DM, T2DM	28	26	Macular pucker, macular hole	None	Vitreous	ELISA	TIMP-1, CCN2, VEGF, TGF-β2, MMP-2, MMP-9
Vidhya et al. 2013	India	No patient details provided	Not specified	29	11	Macular hole	PRP	Vitreous	ELISA	APN, PEDF, IGF-1, VEGF
Vogels et al. 2013	Netherlands	No patient details provided	Not specified	28	26	Macular pucker, macular hole	None	Vitreous	ELISA	TIMP-1, TGF-β2, CTGF, VEGF
Abu El-Asrar et al. 2014	Saudi Arabia	Patients with PDR with vitrectomy for retinal detachment vitreous hemorrhage	Not specified	30	30	RD	None	Vitreous	ELISA	OPN, Syndecan-1, VEGF
Cancarini et al. 2014	Italy	Mean age 62.9, 50.9% male	T2DM	33	20	Macular pucker, macular hole	Intravitreal bevacizumab	Both	ELISA	EPO, VEGF
Comyn et al. 2014	United Kingdom	No patient details provided	Not specified	30	0	No control	Intravitreal ranibizumab	Vitreous	Not specified	IL-1α, VEGF
Dai et al. 2014	China	91% on long-term regular insulin, most with previous PRP, mean age 58, 56% male	Not specified	32	26	Macular hole, ERM	None	Vitreous	Bead-based multiplex immunoassay	MCP-1, MIP-1β, CCL11, CCL17, CCL19, CXCL9, CXCL10, TGF-β1, TGF-β2, TGF-β3, VEGF
Hsu et al. 2014	China	Study of paper-based ELISA, no specifics on patient population	Not specified	14	13	Cataract surgery	None	Aqueous	Paper ELISA (P-ELISA)	VEGF
Loukovaara et al. 2014	Finland	PDR patients with or without tractional RD, mean age 43.8 ± 18.2, 39.7% male	T1DM, T2DM	31	150	Macular hole, RD	None	Vitreous	ELISA	HIF-1α
Mao et al. 2014	China	Patients with vitrectomy, hemorrhage within 2 months, or ocular inflammation or photocoagulation within 3 months were excluded, mean age 55.1 ± 13.2, 46.2% male	IDDM	26	8	Cadaveric	None	Vitreous	ELISA	IL-1β, IL-6
Marra et al. 2014	United States	No patient details provided	Not specified	NA	NA	Macular hole, ERM	None	Vitreous	magnetic bead-based assay	G-CSF, sCD40L, Endoglin, IL-6, PlGF, VEGF-D, leptin, IL-8, VEGF-A, TIE-2, EGF, HB-EGF, TNF-α
Mesquita et al. 2014	Portugal	No patient details provided	Not specified	NA	NA	RD	None	Vitreous	ELISA	VEGF-B

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Murugeswari et al. 2014	India	Patients with other forms of retinopathy and other systemic infective/ autoimmune/other inflammatory disease were excluded, mean age 54.2 ± 7.8, 84.6% male	T2DM	10	4	Macular hole	None	Vitreous	ELISA, biochip array	IL-2, IL-4, IL-6, IL-8, IL-10, IL-1α, IL-1β, IFN-γ, VEGF, TNF-α, MCP-1, EGF
Nakamura et al. 2014	Japan	Mean age 58.4 ± 12.1, 50% male	Not specified	20	19	Macular hole	None	Vitreous	ELISA	Metallothioneins, VEGF
Ran et al. 2014	China	Vitreous samples with hemorrhage were excluded, mean age 62.2 ± 2.3	Not specified	20	20	RD	None	Vitreous	ELISA	VEGF
Schoenberger et al. 2014	United States	Exclusion criteria of previous vitrectomy, prior intravitreal injection within 3 months, and previous enrollment of the fellow eye, mean age 52 ± 10	Not specified	10	0	No control	topical ketorolac tromethamine 0.45%	Both	Bead-based multiplex immunoassay	Eotaxin, Flt-3L, GRO, IFN-γ, IL-1β, IL-6, IL-8, IL-10, IL-12p40, IP-10, MCP-1, TNF, VEGF, RANTES, PDGF-AA, PDGF-AB
Semeraro et al. 2014	Italy	Exclusion criteria of previous vitrectomy or other ophthalmic surgery or laser therapy within the previous 3 months, mean age 62.1 ± 10.4, 55% male	T2DM	33	20	Macular hole, macular pucker	None	Both	ELISA	VEGF
Shchuko et al. 2014	Not specified	Active PDR, mean age 56	Not specified	6	NA	Not specified	None	Aqueous	ELISA	IL-6, IL-8, MCP-1, VEGF
Song et al. 2014	China	Exclusion criteria included VH secondary to ocular disease other than diabetes, previous vitreous surgery, or any intravitreal injection before their current surgery, mean age 59.6 ± 4.8, 46.2% male	T2DM	30	15	Macular hole, ERM	None	Vitreous	ELISA	IL-18, VEGF
Suzuki et al. 2014	Japan	Exclusion criteria of different pre-operative severity of retinopathy between both eyes, neovascular glaucoma or tractional RD in at least 1 eye, type 1 diabetes mellitus, previous intraocular surgery, systemic and/or ocular inflammatory disease, mean age 46.6 ± 16.7, 50% male	T2DM	8	0	No control	Intravitreal bevacizumab	Vitreous	Bead-based multiplex immunoassay	IL-1β, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12p70, IL-13, IL-15, IL-17, Eotaxin, bFGF, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1, MIP-1α, MIP-1β, PDGF-BB, RANTES, TNF-α, VEGF
Takahashi et al. 2014	Japan	No patient details provided	Not specified	96	41	Macular hole	Photocoagulation	Vitreous	ELISA	Periostin, VEGF, MCP-1
Takeuchi et al. 2014a	Japan	Mean age 55 ± 10.7, 73.8% male	Not specified	60	29	RD, ERM	None	Vitreous	suspension bead array	IL-1β, IL-4, IL-6, IL-10, IL-17A, IL-17F, IL-21, IL-22, IL-23, IL-25, IL-31, IL-33, IFN-γ, sCD40L, TNF-α
Takeuchi et al. 2014b	Japan	No patient details provided	Not specified	35	21	Macular hole, ERM, RD	None	Vitreous	Bead-based multiplex immunoassay	IL-1β, IL-4, IL-6, IL-10, IL-17A, IL-17F, IL-21, IL-22, IL-23, IL-25, IL-31, IL-33, sCD40L, TNF-α, IFN-γ
Teague et al. 2014	United States	No patient details provided	Not specified	NA	NA	Macular hole, ERM, vitreous floaters	None	Vitreous	Multiplex assay	PlGF, VEGF-A, TNF-α, TIE-2, Prolactin, bFGF, EGF

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Ucgun et al. 2014	Turkey	Also measured central macular thickness	Not specified	21	21	Nondiabetic	None	Vitreous	ELISA	IFN-γ, TNF-α, MMP-2, MMP-9
Wang et al. 2014	China	Exclusion criteria of prior vitreoretinal surgery or anti-VEGF injection, uveitis or ocular inflammation, previous PRP, iris or angle neovascularization, and elevated intraocular pressure (IOP), mean age 61.7 ± 12.3, 48% male	Not specified	50	56	Macular hole, preretinal membrane	None	Vitreous	ELISA	VEGF
Yabanoglu et al. 2014	Turkey	Excluded patients with a history of previous vitreoretinal surgery, intravitreal therapy, vitreous hemorrhage in the last 2 months, and photocoagulation in the last 3 months, mean age 58 ± 10.5, 40.9% male	T2DM	22	10	Macular hole, ERM	None	Vitreous	Bead-based multiplex immunoassay	TNF-α, IL-6, VEGF, IL-1β, IL-8, IL-17, MCP-1, IL-1Ra, IL-10
Abu El-Asrar et al. 2015a	Saudi Arabia	Patients with PDR with vitrectomy for retinal detachment vitreous hemorrhage	Not specified	33	27	RD	None	Vitreous	ELISA	VEGF, Syndecan-1
Abu El-Asrar et al. 2015b	Saudi Arabia	Active PDR in 5 patients and inactive PDR in 9 patients, mean age 57.5 ± 14.4, 64.7% male	IDDM, NIDDM	34	23	RD	None	Vitreous	ELISA	TNFSF15, TWEAK, sICAM-1
Brzovic-Saric et al. 2015	Croatia	Excluded patients with previous intravitreal steroids or anti-VEGF therapy, on systemic corticosteroid therapy or cytostatics, mean age 68.9 ± 11.65	T2DM	37	50	Macular hole, ERM, RD	None	Vitreous	ELISA	VEGF
Chernykh et al. 2015	Russia	Excluded acute or exacerbation of chronic inflammatory ocular diseases, primary open-angle glaucoma, systemic autoimmune disorders, and tumors of any localization, mean age 50.5 ± 3.2, 42.1% male	T1DM, T2DM	38	25	RD	None	Vitreous	ELISA	VEGF, PEDF, MCP-1, IL-4, IL-6, IL-8, IL-10, IL-17 A, sIgA
Gao et al. 2015	China	Exclusion criteria included photocoagulation or vitreous hemorrhage within 3 months, vitreoretinal surgery within 2 years, and past history of ocular inflammation, rubeosis iridis, and rhegmatogenous retinal detachment, mean age 54.3 ± 10.1, 40% male	Not specified	30	25	Macular hole, ERM	None	Vitreous	ELISA	LRP6, VEGF
Hassan et al. 2015	United States	No patient details provided	Not specified	NA	0	No control	None	Aqueous	ELISA	PAI-1, VEGF
Katome et al. 2015	Japan	Patients with a history of vitreoretinal surgery were excluded, mean age 51.7	T2DM	50	38	ERM	None	Both	ELISA	VEGF

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Kaviarasan et al. 2015	India	Patients with other systemic disease or undergoing treatments apart from diabetes were excluded, mean age 52 ± 7	T2DM	30	20	Macular hole	None	Vitreous	ELISA	BDNF, LXA-4, IFN-γ, TNF-α, IL-2, IL-4, IL-6, IL-10, VEGF
Kita et al. 2015	United States	Mean age 63.4 ± 2.2, 37.5% male	Not specified	24	17	Macular hole	None	Vitreous	ELISA	VEGF
Kobayashi et al. 2015	Japan	Exclusion criteria included age >80, previous PPV, ocular surgery or PRP within 6 months, intraocular injection within 4 months, and hematologic disease, mean age 57.2 ± 12.6, 61.3% male	T2DM	74	56	Macular hole, ERM	None	Vitreous	ELISA	sCD163, periostin, VEGF
Kovacs et al. 2015	United States	Patients were excluded with choroidal detachments, retinoschisis, history of radiation, dislocation or subluxation of the intraocular lens, ocular trauma, or pretreatment with intravitreal or periocular steroids, mean age 65 ± 13.6, 41.1% male	Not specified	29	29	Macular hole, ERM	None	Vitreous	Magnetic bead-based assay	Angiopoietin, EGF, Endoglin, bFGF, G-CSF, HB-EGF, HGF, IGFBP-1, PDGF, PlGF, sEGFR, sHER2/neu, sVEGFR-1, sVEGFR-2, TGF-α, TIE-2, VEGF-A, VEGF-C, VEGF-D, IL-18, IL-6, IL-8, PECAM-1, sCD40L, SCF, sFASL, sIL-6Ra, TNF-α, Follistatin, Leptin, Osteopontin, PAI-1, Prolactin, uPA
Li et al. 2015	China	Exclusion criteria included previous ocular surgery, a history of ocular inflammation, photocoagulation within 3 months, renal hematological diseases, uremia, prior chemotherapy, and chronic pathologies other than diabetes, mean age 53.9 ± 8.5, 52.6% male	T1DM, T2DM	19	15	Macular hole	Intravitreal bevacizumab	Vitreous	ELISA	VEGF, bFGF
Mesquita et al. 2015	Portugal	No patient details provided	Not specified	17	17	RD	None	Vitreous	ELISA	PlGF
Mohammad et al. 2015	Saudi Arabia	Indications for vitrectomy were traction retinal detachment, and/or non-clearing vitreous hemorrhage	Not specified	48	34	RD	None	Vitreous	ELISA	IL-1β, HMGB1
Rusnak et al. 2015	Czech Republic	PDR patients had vitreous hemorrhage, tractional RD, exudative maculopathy, and/or fibroproliferation	Not specified	10	50	Cataract surgery	None	Vitreous	Multiplex xMAP	EGF, IL-6, VEGF, TNF-α, IL-8, IP-10, MCP-1, PDGF AA, TGF-β1, fractalkine, PDGF-AB, PDGF-BB, IL-10, IFN-γ, bFGF, CNTF, BDNF, RANTES
Takeuchi et al. 2015a	Japan	Exclusion criteria of previous vitrectomy, prior intravitreal therapies, trauma, and infectious endophthalmitis, mean age 57 ± 13.7, 72% male	T2DM	25	26	Macular hole	None	Vitreous	suspension bead array	IL-1β, IL-4, IL-6, IL-10, IL-17A, IL-17F, IL-21, IL-22, IL-23, IL-25, IL-31, IL-33, IFN-γ, sCD40L, TNF-α
Takeuchi et al. 2015b	Not specified	No patient details provided	Not specified	NA	NA	Macular hole, ERM	None	Vitreous	Not specified	IL-4, IL-6, IL-10, IL-17A, IL-21, IL-22, IL-31, TNF-α, sCD40L, IFN-γ

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Tanaka et al. 2015	Japan	Mean age 54.8 ± 10.6	T2DM	60	0	No control	None	Vitreous	Bio-Plex Pro Human Th17 Cytokine Assays	IL-6
Wan et al. 2015	China	Subjects were excluded if they had chronic systemic disease, cancers, ocular disorders, previous intraocular surgery or laser treatment, photocoagulation, and intravitreal hemorrhages within 3 months, mean age 57.3 ± 11, 47.4% male	T2DM	95	65	RD	None	Vitreous	ELISA	Omentin-1
Xu et al. 2015	China	Twelve of the PDR patients had prior panretinal photocoagulation, mean age 52.1 ± 1.5, 44.1% male	Not specified	34	37	Macular hole, ERM, RD	None	Vitreous	Bead-based multiplex immunoassay	IL-1β, IL-6, IL-8, IL-10, IL-18, CCL1, MCP-1, CCL3, CCL4, CCL7, CCL8, CXCL4, CXCL5, CXCL6, CXCL9, IP-10, VEGF, VEGF-R1 VEGF-R2, TNF-α, IFN-γ, sCD200
Yoshida et al. 2015a	Japan	Exclusion criteria of age >80 years, renal or hematologic disease, uremia, previous chemotherapy, and chronic disease other than diabetes, mean age 61.9 ± 7.6, 57.4% male	Not specified	61	39	Macular hole, ERM	None	Vitreous	ELISA	M-CSF, sCD163, VEGF, GM-CSF, IL-4, IL-13
Yoshida et al. 2015b	Japan	Exclusion criteria of age >80 years, renal or hematologic disease, uremia, previous chemotherapy, and chronic disease other than diabetes, mean age 56.8 ± 10.5, 66.7% male	Not specified	36	57	Macular hole	PPV	Vitreous	ELISA	MCP-1, IL-6, IL-8, VEGF
Yu et al. 2015	China	Patients with previous intraocular surgery, other ocular or systemic disorders, or obvious vitreal hemorrhage within 3 months were excluded, mean age 55.2 ± 12.1, 51.1% male	T2DM	90	62	RD	None	Vitreous	ELISA	Osteoprotegerin
Zhao et al. 2015	China	Patients receiving intravitreal injection treatment, who had active intraocular inflammation, recent cerebral vascular accident or myocardial infarction, or had other systemic diseases which precluded vitrectomy were excluded	Not specified	8	6	ERM	None	Vitreous	ELISA	Pro-IL-1β, IL-1β
Zhu et al. 2015	China	Mean age 57.6 ± 9.2, 44.8% male	Not specified	24	14	Macular hole, ERM	Anti-VEGF injections	Vitreous	ELISA	PTN, VEGF
Abu El-Asrar et al. 2016a	Saudi Arabia	No patient details provided	Not specified	33	27	Nondiabetic	None	Vitreous	ELISA	Syndecan-1, VEGF
Abu El-Asrar et al. 2016b	Saudi Arabia	No patient details provided	Not specified	32	23	RD	None	Vitreous	ELISA	VEGF, thrombin, MMP- 1

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Chen et al. 2016a	China	Exclusion previous intraocular surgery, earlier intravitreal therapies, photocoagulation during the preceding 3 months, uveitis, trauma, vitreous hemorrhage, and retinal detachment, mean age 60.6 ± 5.1, 56.6% male	T2DM	53	51	Cataract surgery	None	Aqueous	Bead-based multiplex immunoassay	IL-6, sIL-6R, sgp130
Delil et al. 2016	Turkey	No patient details provided	Not specified	23	15	Nondiabetic	None	Vitreous	ELISA	VEGF
Forooghian et al. 2016	Canada	Exclusion criteria included VH secondary to ocular disease other than diabetes, mean age 52 ± 13, 43% male	Not specified	14	0	No control	Intravitreal ranibizumab	Aqueous	ELISA	VEGF, PlGF, IL-8, TGF-β2
Gao et al. 2016	China	Exclusion criteria included PRP or PDT in the preceding 3 months, anti-VEGF agents or steroid within past 6 months, prior vitreoretinal surgery, mean age 55.57 ± 9.51, 38.1% male	Not specified	45	28	Macular hole	None	Vitreous	ELISA	Wnt3a, VEGF
Ghodasra et al. 2016	United States	Mean age 62, 55% male	Not specified	17	14	Macular hole, ERM, vitreous floaters	None	Vitreous	Cytometric bead assay	MCP-1, CCL3, CCL4, RANTES, MCP-3, CXCL1, IP-10, ADAM11, fractalkine, eotaxin, EGF, FGF, fms-related tyrosine kinase 3 ligand, G-CSF, GM-CSF, IFN-α2, INF-γ, IL-1ra, IL-1-a, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17A, PDGF-A, PDGF-B, sCD40L, TGF-α, TNF-α, TNF-β, VEGF
Inafuku et al. 2016	Japan	Investigating relation of N-glycans with VEGF, mean age 56.1 ± 6.7, 36.3% male	Not specified	18	17	Macular hole, ERM	None	Vitreous	Modified glycoblotting, ELISA	VEGF
Jiang et al. 2016	China	Patients who had previously undergone retinal photocoagulation, intravitreal anti-VEGF injection or vitreoretinal surgery were excluded, mean age 59.8 ± 9.15, 45.7% male	T2DM	35	30	Macular hole, ERM	None	Vitreous	ELISA	TNFSF15, VEGF
Kobayashi et al. 2016	Japan	Mean age 59 ± 10.2, 58.9% male	Not specified	133	41	Macular hole	None	Vitreous	ELISA	Tenascin-C, periostin, IL-13
Li et al. 2016a	China	PDR patients with vitreous hemorrhage or tractional RD, exclusion criteria of previous intravitreal injection, anti-VEGF agents, ocular or systemic inflammatory diseases, mean age 55.6 ± 8.2, 52.4% male	T2DM	38	25	Macular pucker, ERM	None	Vitreous	Western Blot	Chemerin, VEGF

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Lu et al. 2016	China	Patients were excluded if they had received treatment for ocular diseases, mean age 54.03 ± 4.58, 42.9% male	Not specified	35	14	Macular hole	None	Vitreous	ELISA	ANGPTL-4, VEGF
Nandakumar et al. 2016	United States	No patient details provided	Not specified	35	28	Macular hole, ERM, vitreomacular traction, vitreous floaters	None	Vitreous	Bead-based multiplex immunoassay	PlGF, VEGF-A, sCD401, PAI-1, sVEGFR-1
Oubaha et al. 2016	Canada	Mean age 65 ± 13.4, 30% male	Not specified	10	10	Macular hole, ERM, RD	None	Vitreous	Luminex assay	PAI-1, IL-6, IL-8, VEGF-A
Sassa et al. 2016	Japan	High risk PDR without triamcinolone or anti-VEGF treatment, also excluded previous intraocular surgery or inflammation, RD, age >80 years, renal and hematologic diseases, uremia, and prior chemotherapy, mean age 56.4 ± 10, 57.1% male	T2DM	21	0	No control	PPV	Vitreous	ELISA	MCP-1, VEGF
Suzuki et al. 2016a	Japan	Patients with and without pre-operative pan-retinal photocoagulation	Not specified	64	0	No control	PRP	Vitreous	suspension bead array	IL-1β, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, IP-10, Eotaxin, bFGF, G-CSF, GM-CSF, IFN-γ, MCP-1, MIP-1α, MIP-1β, PDGF-BB, RANTES, TNF-α, VEGF
Suzuki et al. 2016b	Japan	Patients were excluded for prior injection of an anti-VEGF agent, triamcinolone acetonide injection within 6 months, photocoagulation within 3 months, complications due to neovascular glaucoma, or followed-up less than 6 months, mean age 54.7 ± 15, 47.4% male	Not specified	45	0	No control	None	Vitreous	suspension bead array	IL-1β, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, Eotaxin, bFGF, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1, MIP-1α, MIP-1β, PDGF-BB, RANTES, TNF-α, VEGF
Takahashi et al. 2016	Japan	Patients with RRD secondary to trauma or other disorders or those associated with diabetes mellitus were excluded, mean age 61.2 ± 9.3, 46.4% male	Not specified	55	28	RD	None	Vitreous	Bead-based multiplex immunoassay	IL-1β, IL-1 IL-1ra, IL-2, IL- 4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, Eotaxin, bFGF, G-CSF, GM-CSF, IFN-α, IFN-γ, MCP-1, MIP-1α, MIP-1β, IP-10, PDGF, RANTES, VEGF
Tamaki et al. 2016	Japan	Patients were excluded if they had refractory neovascular glaucoma or vitreous hemorrhage, mean age 52 ± 16, 56% male	Not specified	27	23	Macular hole, ERM	None	Vitreous	ELISA	MCP-1, PTX3, SAP
Xing et al. 2016	China	Exclusion criteria included end-stage renal disease, cardiac arrhythmia, inflammatory conditions, recent stroke (<3 months), myocardial infarction, and ocular surgery or injections, mean age 55.9 ± 11.5, 40% male	Not specified	10	7	Macular hole, preretinal membrane	None	Vitreous	ELISA	Kallistatin

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Yan et al. 2016	China	The exclusion criteria included prior cataract surgery, neovascular glaucoma, vitreous hemorrhage within 2 months, HbA1c > 9, systemic inflammatory disease and malignancy, mean age 54.8 ± 7.8, 54.5% male	Not specified	22	22	Idiopathic macular pucker	Intravitreal ranibizumab	Vitreous	ELISA	ICAM-1, VEGF
Zhao et al. 2016	China	In the PDR group, one patient PRP 1 year ago, two patients were treated with retinal photocoagulation three or five times a year, and three were treated with iodized, no previous anti-VEGF, mean age 58.1 ± 9.5, 40% male	Not specified	10	8	Macular hole, ERM	None	Vitreous	ELISA	IL-37, VEGF-A, Ang-2
Abu El-Asrar et al. 2017a	Saudi Arabia	Active PDR was present in 25 patients, and inactive PDR was present in 22 patients, mean age 52.1 ± 11.4, 68.1% male	IDDM, NIDDM	47	19	RD	None	Vitreous	ELISA	HMGB1, 8-OHDG, sVap-1
Abu El-Asrar et al. 2017b	Saudi Arabia	Active PDR was present in 20 patients, and inactive PDR was present in 20 patients	IDDM, NIDDM	40	19	RD	None	Vitreous	ELISA	EMMPRIN, VEGF, MMP-1, MMP-9
Abu El-Asrar et al. 2017c	Saudi Arabia	Vitrectomy for tractional RD and/or non-clearing vitreous, no patient details provided	Not specified	47	28	RD	None	Vitreous	ELISA	VEGF, OPG, sRANKL, RANK, sTRAIL
Abu El-Asrar et al. 2017d	Saudi Arabia	Indications for vitrectomy were tractional RD and/or non-clearing vitreous hemorrhage	Not specified	47	28	RD	None	Vitreous	ELISA	OPG, VEGF, MCP-1
Barliya et al. 2017	Israel	Exclusion criteria were previous vitrectomy or combined cataract and pars plana vitrectomy, mean age 55 ± 11, 83% male	Not specified	12	10	Macular hole, ERM	None	Vitreous	ELISA	MPO
Chen et al. 2017a	China	Patients were excluded if previous intraocular surgery, earlier intravitreal therapies, photocoagulation in the preceding 3 months, uveitis, trauma, vitreous hemorrhage, or retinal detachment, mean age 58.4 ± 7.2, 65.4% male	T2DM	52	51	Cataract surgery	None	Aqueous	Bead-based multiplex immunoassay	IL-1ra, IL-1β, IL-1α, IL-2, IL-4, IL-5, IL-6, IL- 7, IL-8, IL-9, IL-10, IL-12 p70, IL-13, IL-15, IL-17 A, IL-18, IL-21, IL-22, IL-23, IL-27, IL-31, TNF-α, TNF-β, IFN-γ, IFN-α, BDNF, GM-CSF, LIF, SCF, Eotaxin, GRO, IP-10, MCP-1, MIP-1α, MIP-1β, RANTES, SDF-1α, EGF, bFGF, HGF, β-NGF, PDGF-BB, PlGF, VEGF-A, VEGF-D
Chen et al. 2017b	China	Active PDR was present in 31 patients, inactive PDR was present in 15 patients, mean age 57.6 ± 5.5, 30.3% male	T2DM	46	19	Macular hole	PRP	Vitreous	Bio-Plex Pro Human Th17 Cytokine Assays	VEGF
Ehrlich et al. 2017	Israel	Excluded patients with previous vitrectomy, mean age 61 ± 13, 50% male	Not specified	20	26	Macular hole, ERM	None	Vitreous	ELISA	TAT, IL-6

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Gomaa et al. 2017	Egypt	Exclusion criteria for both groups included patients with other systemic diseases, PRP, or intravitreal anti-VEGF in the last 6 months, previous PPV, presence of rubeosis iridis, neovascular glaucoma, rhegmatogenous retinal detachment, retinal vascular occlusion, or a history of intraocular inflammation, 39% male	T1DM, T2DM	29	30	Macular hole	None	Vitreous	ELISA	VEGF
Houssen et al. 2017	Egypt	Excluded patients with uncontrolled hypertension or other systemic disease, dense cataract, previous laser or intraocular injection, mean age 65.2 ± 5	T2DM	20	20	Nondiabetic	None	Aqueous	ELISA	IL-27
Hua et al. 2017	United States	No patient details provided	Not specified	35	28	Not specified	None	Vitreous	ELISA	VEGF-A, PlGF, PAI-1, IL- 8
Kahtani et al. 2017	Saudi Arabia	Active PDR cases were classified according to the administration of preoperative bevacizumab within 7 days of surgery	T2DM	46	21	RD, Macular hole, vitreomacular traction, dropped nucleus	Intravitreal bevacizumab	Vitreous	ELISA	PlGF, VEGF
Katagiri et al. 2017	Japan	Subjects were excluded for epiretinal membrane and a history of vitreous surgery or intraocular injection, mean age 57, 68% male	Not specified	25	0	No control	None	Vitreous	ELISA	sRAGE, VEGF
Klaassen et al. 2017	Netherlands	Excluded patients with pan-retinal laser treatment or cataract surgery within 2 months, previous vitrectomy surgery, previous steroid therapy within 1 year, and anti-VEGF therapy within 3 months, mean age 52.3 ± 10.1, 50% male	T2DM	16	7	Floaters	None	Vitreous	Quantibody array	APN, Ang-1, Ang-2, AR, BDNF, bFGF, BMP-2, BMP-5, b-NGF, E-Selectin, Galectin-3, GDF-15, GDNF, HGF, ICAM-1, ICAM-3, IGFBP-1, IGFBP-2, IGFBP-3, IGFBP-4, IGFBP-5, IGFBP-6, IGF-I, IGF-IR, IGF-II, IGF-IIR, NCAM-1, PDGF-Ra, PDGF-Rb, PDGF-AA, PDGF-AB, PDGF-BB, PlGF, Prolactin, TARC, TGF-β1, TGF-β2, Thrombospondin-1, TIMP-1, TIMP-4, TPO, VCAM-1, VEGF, WIF-1, WISP-1
Loukovaara et al. 2017	Finland	Five PDR patients had received intravitreal anti-VEGF treatment prior to surgery, mean age 45.1 ± 3.1, 39.1% male	T1DM, T2DM	23	0	No control	None	Vitreous	ELISA	NLRP3, ASC, Caspase-1, IL-1β, IL-18, TNF-α, IL-6, IFN-γ, VEGF
Lu et al. 2017	China	Patients were excluded if they had received treatment for ocular diseases, mean age 56.6 ± 4.5, 46.4% male	Not specified	28	12	Macular hole	None	Vitreous	ELISA	ANGPTL-8, VEGF

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Masuda et al. 2017	Japan	For the eyes with PDR, 15 had an intravitreal injection of bevacizumab (IVBβ) and 24 eyes did not have an IVB before collection of vitreous samples, mean age 64.4 ± 10.1, 50% male	Not specified	24	40	Macular hole	Intravitreal bevacizumab	Vitreous	ELISA	VEGF
Megarity et al. 2017	United States	No patient details provided	Not specified	NA	NA	Not specified	Anti-VEGF injections	Vitreous	ELISA	VEGF, ANGPT2, EPO, ANGPTL4
Mesquita et al. 2017	Portugal	No patient details provided	Not specified	8	4	Vitreomacular traction	None	Vitreous	ELISA	VEGF-A, VEGF-B
Mutlu et al. 2017	Turkey	Patients with glaucoma, pseudoexfoliation, active ocular inflammation, history of ocular surgery, previous intravitreal corticosteroid or anti-VEGF injections, and argon laser focal, grid or panretinal photocoagulation within last 6 months were excluded, mean age 65.6 ± 7.2, 50% male	T2DM	15	29	Cataract surgery	None	Aqueous	ELISA	PTX-3
Ridano et al. 2017	Argentinian	Patients had a diabetes duration of at least 5 years, mean age 66, 44.4% men	T2DM	9	6	Cataract surgery	None	Aqueous	ELISA	Galectin-1
Takeuchi et al. 2017a	Japan	Exclusion criteria included previous vitrectomy, prior intravitreal therapies, trauma, and infectious endophthalmitis, mean age 54.9 ± 13.2, 66.7% male	Not specified	27	24	ERM	None	Vitreous	Bio-Plex Pro Human Th17 Cytokine Assays	IL-1β, IL-4, IL-6, IL-10, IL-17A, IL-17F, IL- 21, IL-22, IL-23, IL-25, IL-31, IL-33, IFN-γ, sCD40L, TNF-α
Takeuchi et al. 2017b	Japan	Exclusion criteria were previous vitrectomy, prior intravitreal therapies, trauma, uveitis, and infectious endophthalmitis, mean age 56.8 ± 12.4, 77.4% male	T2DM	31	0	No control	None	Both	Bio-Plex Pro Human Th17 Cytokine Assays	IL-1β, IL-4, IL-6, IL-10, IL-17A, IL-17F, IL-21, IL-22, IL-23, IL-25, IL-31, IL-33, IFN-γ, sCD40L, TNF-α
Takeuchi et al. 2017c	Japan	No patient details provided	T2DM	31	0	No control	None	Both	Cytometric bead assay	IL-1β, IL-4, IL-6, IL- 10, IL-17A, IL-17F, IL-21, IL-22, IL-23, IL-25, IL-31, IL-33, IFN-γ, sCD40L, TNF-α
Tamaki et al. 2017	Japan	No patient details provided	Not specified	19	13	Macular hole	None	Vitreous	ELISA	PTX-3, TNF-α, IL-1β
Vingolo et al. 2017	Italy	Exclusion criteria were prior treatment with steroid or non-steroid anti-inflammatory drugs, history of infections, fever, cancer or organ failure, thrombotic events, intraocular or vitreoretinal surgery within 6 months, and history of intravitreal injection therapies, mean age 63.3 ± 12.5, 44.4% male	T2DM	9	11	Macular hole, ERM, RD	None	Vitreous	Radioimmunoassay (RIA)	ET-1, ADM, VEGF-A

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Wakabayashi et al. 2017	Japan	Exclusion criteria were a history of previous vitreoretinal surgery except laser photocoagulation to treat PDR, prior anti-VEGF injection, preexisting neovascular glaucoma, and intraoperative use of silicone oil, mean age 53, 57.4% male	T1DM, T2DM	85	0	No control	PPV	Vitreous	ELISA	VEGF
Wang et al. 2017	China	Exclusion criteria included previous ophthalmic surgery in either eye, previous intravitreal injection, usage of clopidogrel or coumadin, uncontrolled hypertension, cardiac, renal, or liver disease, mean age 54.6 ± 13.1, 51% male	T1DM, T2DM	39	24	Cataract surgery, Macular hole	None	Both	ELISA	IL-6, MCP-1
Wei et al. 2017	China	Patients with other retinal diseases, a history of ocular surgery (including cataract extraction), who had received more than one IVI or if the injections occurred ≥7 days before surgery, and who underwent photodynamic therapy were excluded, mean age 58.9, range 44-72, 47.6% male	T1DM, T2DM	21	0	No control	Intravitreal ranibizumab	Vitreous	ELISA	VEGF, VEGFR-1, VEGFR-2
Wu et al. 2017	China	Patients were excluded with severe diabetic complications, such as nephropathy, ketoacidosis, or hyperosmotic coma, major systemic disorders, a history of ocular surgery including intravitreal injections or receiving laser treatment within 12 months, mean age 67, 42.9% male	T2DM	14	10	Cataract surgery	None	Aqueous	cytometric bead array	IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IFN-γ, TNF-α, VEGF
Yoshida et al. 2017	Japan	Exclusion criteria of age >80, previous history of ocular trauma or pars plana vitrectomy, ocular surgery or PRP within 6 months, hematologic disease, uremia, chemotherapy and epilepsy, mean age 55.4 ± 14.4, 62.8% male	Not specified	129	110	Nondiabetic	Vitrectomy	Vitreous	cytometric bead array	MCP-1, IL-6, IL-8, VEGF

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Yu et al. 2017	China	Excluded patients with systemic and recent infection, previous intraocular surgery, uveitis, preoperative VEGF inhibitors, mean age 54.2 ± 11.3, 40% male	Not specified	10	9	Macular hole, ERM	None	Vitreous	ELISA	Ang-1, Ang-2, IL-6, HGF, VEGF, MMP-9, PIGF, UPAR, Timp-1, ANGPTL4, ENA-78, GRP, HGF, IL-8, IP-10, Leptin, LIF, MCP-1, PDGF-BB, RANTES, TGF-β1, Timp-2, Angiostatin, CXCL-16, FGF-4, Follistatin, G-CSF, I-309, IL-1β, IL-4, IL-12p40, I-TAC, MCP-2, MCP-3, MCP-4, MMP-1, MMP-9, PECAM-1, TGF-β3, VEGFR2, VEGFR3
Zhou et al. 2017	China	Panretinal photocoagulation had been performed in 8 patients at least 4 months prior to inclusion in the study, mean age 51.6 ± 14.2, 55.6% male	T2DM	27	28	Macular hole, ERM	None	Vitreous	ELISA	Slit2
Abu El-Asrar et al. 2018a	Saudi Arabia	Active PDR was present in 20 patients, and inactive PDR was present in 20 patients.	Not specified	40	20	RD	None	Vitreous	ELISA	VEGF, ORP150, TAC
Abu El-Asrar et al. 2018b	Saudi Arabia	Vitrectomy for tractional retinal detachment and/or non-clearing vitreous hemorrhage, mean age 51.8 ± 12.8, 61.8% male	Not specified	34	18	RD	None	Vitreous	ELISA	MMP-9, MMP-14, VEGF
Abu El-Asrar et al. 2018c	Saudi Arabia	Mean age 50.2 ± 9.9, 60% male	IDDM, NIDDM	16	16	RD	None	Vitreous	Western Blot, Immunohistochemistry	MRP-8, MRP-14, ICAM-1
Abu El-Asrar et al. 2018d	Saudi Arabia	Active PDR was present in 19 patients, and inactive PDR was present in 19 patients	Not specified	38	21	RD	None	Vitreous	ELISA	TIMP-1, TIMP-2, TIMP-3, TIMP- 4, MMP-9, VEGF
Chen et al. 2018	China	Excluded patients with infectious diseases or other diabetic complications, prior intraocular procedures or intravitreal treatments, photocoagulation within 3 months, uveitis, trauma, vitreous hemorrhage, retinal detachment, or immunosuppressive drugs, mean age 60.6 ± 5.5, 57.1% male	T2DM	21	22	ERM	None	Vitreous	ELISA	IL-1β, IL-18
Cho et al. 2018	United States	No patient details provided	Not specified	NA	NA	Cataract surgery	None	Vitreous	ELISA	VEGF, VCAM-1, IL-15, IL-16, SAA, bFGF
Feng et al. 2018a	China	Excluded patients on anticoagulants, with abnormal liver or kidney function, with type I diabetes, and receiving treatment in the past year, mean age 59.3 ± 7.2, 45% male	T2DM	19	40	Diabetic without DR	None	Aqueous	ELISA	IL-1β, IL-6, IL-8, IL-17, TNF-α

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Feng et al. 2018b	China	Patients with and without IVB treatment, exclusion criteria included previous ocular surgery, anti-VEGF therapy or panretinal photocoagulation within 6 months and a history of tumors or other systemic diseases treated with anti-VEGF therapy, mean age 54.7 ± 12.1, 57.1% male	Not specified	14	8	Cataract surgery	Intravitreal bevacizumab	Aqueous	Luminex x-MAP suspension array	VEGF, IL-6, IL-8, IL-1β, MCP-1, TNF-α, TGF-β, bFGF
Fujita et al. 2018	Japan	No patient details provided	Not specified	8	15	Cataract surgery	None	Aqueous	beads-array system	IL-4, IL-6, IL-8, IL-10, GM-CSF, IFN-γ, TNF-α
Gucciardo et al. 2018	Finland	Mean age 37.8 ± 14.5, 43.9% male	T1DM, T2DM	53	0	No control	None	Vitreous	ELISA	VEGF-A, VEGF-C, TGF-β, bFGF
Katagiri et al. 2018	Japan	Excluded patients with a history of vitreous surgery or intraocular injection, mean age 56.9, 60% male	Not specified	25	0	No control	None	Vitreous	ELISA	VEGF, IL-8, Leptin, PlGF
Kokubun et al. 2018	Japan	Previous surgery was at least one year before the aqueous sample collection and none of the patients in this study underwent any other type of intraocular surgery, mean age 67.4 ± 6.4, 66.7% male	Not specified	9	21	Cataract surgery	None	Aqueous	Bead-based multiplex immunoassay	IL-1ra, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, IFN-γ, TNF-α, MCP-1, MIP-1α, MIP-1β, RANTES, IL-8, IP-10, VEGF, bFGF, G-CSF, GM-CSF, PDGF-BB
Mesquita et al. 2018a	Portugal	None of the patient had undergone either intravitreal injections or laser treatments within 3 months, and diabetic therapy remained unchanged for at least 3 months, mean age 68 ± 11.9	T1DM, T2DM	8	3	Vitreomacular traction	None	Vitreous	ELISA	VEGF-A, VEGF-B
Peng et al. 2018	United States	No patient details provided	Not specified	5	10	ERM, vitreous opacity	None	Vitreous	PCR	VEGF, IL-6, MCP-1
Raczynska et al. 2018	Poland	SD-OCT data available, patients with and without prior anti-VEGF injections, mean age 52.4 ± 17.8, 53.3% male	T1DM, T2DM	15	10	RD, ERM, vitreous hemorrhage, intraocular lens subluxation	Intravitreal aflibercept	Vitreous	Cytometric bead array	IL-6, IL-8, IL-12p70, TNF, IL-10, IL-1β
Sahajpal et al. 2018	India	No patient details provided	Not specified	33	12	Nondiabetic	None	Vitreous	ELISA	VEGF
Schori et al. 2018	Switzerland	Exclusion criteria were glaucoma, intraocular surgery within the last 6 months, ocular medications other than lubricants, intraocular inflammation, myopia of more than 6 diopters spherical equivalent, any other ocular vascular disease, previous retinal detachment, previous vitrectomy, and retinal degenerative disease, mean age 59.3 ± 14.4, 44.4% male	Not specified	9	9	ERM	None	Vitreous	ELISA	VEGF-A, VEGFR-1

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Srividya et al. 2018	India	Excluded patients with prior vitreoretinal surgery, intravitreal anti-VEGF and/or steroids, laser, intra-ocular surgery in the last 6 months, connective tissue disorders, inflammatory bowel diseases, myocardial infarction, and patients on anti-platelets, anti-inflammatory, or immune modulatory medication, mean age 55.4, 85.7% male	Not specified	7	6	Macular hole	None	Vitreous	Bead-based multiplex immunoassay	IL-1β, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12p70, IL-13, IL-15, IL-17A, bFGF, Eotaxin, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1, MIP-1α, MIP-1β, PDGF-BB, RANTES, TNF-α, VEGF
Tsai et al. 2018a	Germany	Excluded patients with current or past anti-VEGF therapy, previous vitrectomy or other ocular surgery or laser within 3 months before, steroids within 3 months, and glaucoma, mean age 63.1 ± 12.2, 29.4% male	T1DM, T2DM	10	17	Macular pucker, macular hole	None	Vitreous	ELISA	IL-1β, IL-6, INF-γ
Wang et al. 2018	China	Exclusion criteria consisted of previous PPV in the study eye, prior intravitreal injection within 3 months, co-existent macular, retinovascular, or ocular inflammatory disease, history of ocular trauma, aphakia, presence of an anterior chamber intraocular lens, and previous enrollment of the fellow eye	Not specified	17	17	Non-PDR	None	Vitreous	ELISA	IL-1β, IL-6, IL-18, IFN-γ, TNF-α, VEGF
Yan et al. 2018	China	Exclusion criteria were chronic systemic disease, dialysis, cancer, ocular disorders, intravitreal hemorrhage, or previous intraocular surgery, mean age 57.9 ± 6.2, 52.4% male	T2DM	21	29	ERM	None	Vitreous	ELISA	IL-27, IL-35
Yoshida et al. 2018	Japan	Vitrectomy for prolonged vitreous hemorrhage and tractional RD, mean age 58.8 ± 8.5, 59.5% male	Not specified	23	0	No control	Intravitreal bevacizumab	Vitreous	ELISA	sVAP-1
Zhou et al. 2018	China	Exclusion criteria were extremely high blood pressure, vitreoretinal disease other than DR, markedly reduced kidney and liver function, heart disease, senile macular degeneration, high myopia, retinal vasculitis, and history of retinal laser photocoagulation, intravitreal injection or vitrectomy, mean age 51.7 ± 8.5, 51.9% male	Not specified	18	9	RD	Intravitreal conbercept	Both	ELISA	VEGF, PlGF

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Abu El-Asrar et al. 2019a	Saudi Arabia	No patient details provided	Not specified	29	19	RD	None	Vitreous	ELISA	sCD163, IL-11, VEGF
Abu El-Asrar et al. 2019b	Saudi Arabia	PDR group consisted of 20 patients who had insulin-dependent diabetes mellitus and 16 patients who had non-insulin-dependent diabetes mellitus	Not specified	36	20	RD	None	Vitreous	ELISA	MIF, VEGF, sICAM-1
Artini et al. 2019	Indonesia	Patients were excluded if they had no light perception, NVG with a cause other than DM, history of cerebrovascular or cardiovascular disease, prolonged coagulation parameters, or previous glaucoma surgeries, mean age 54.3 ± 13.7, 58.8% male	Not specified	10	0	No control	Panretinal photocoagulation	Aqueous	ELISA	VEGF
Balogh et al. 2019	Not specified	No patient details provided	Not specified	8	19	ERM	None	Vitreous	Bioplex beads array	IL-6, IL-8, IL-16, IL-18, IFN-γ, MCP-1, MIP-1β, MIF, Eotaxin, IP-10, SDF-1α, SCGF-β, VEGF
Bozkurt et al. 2019	Turkey	Exclusion criteria of extra- or intraocular surgery or laser photocoagulation, retinal detachment, pseudoexfoliation syndrome, glaucoma, uveitis, mature cataract and corneal opacity, hypertension, chronic hepatic disease, chronic pulmonary disease, rheumatic disease, oncologic disease, and chronic renal failure, mean age 65, 60% male	Not specified	20	56	Cataract surgery	None	Aqueous	ELISA	IL-6, VEGF
Chalam et al. 2019	Not specified	No patient details provided	Not specified	NA	0	No control	None	Vitreous	Suspension bead array	VEGF
Comyn et al. 2019	Not specified	No patient details provided	Not specified	30	7	Nondiabetic	Intravitreal ranibizumab	Vitreous	multiplex bead analysis	IL-1α, IL-4, IL-6, IL-8, IP-10, MCP-1, MDC, Flt-3, VEGF
Dan-Brezis et al. 2019	Israel	Exclusion criteria were previous vitrectomy or combined cataract and pars plana vitrectomy, mean age 57.9 ± 9.2, 60% male	Not specified	20	28	Macular hole, ERM	None	Vitreous	ELISA, Sandwich-based antibody array	VEGF, P-selectin, IL-8
Jung et al. 2019	Korea	Exclusion criteria were pharmacologic intervention or laser photocoagulation of study eye within 6 months or fellow eye within 3 months, prior ocular surgery, and systemic inflammatory disease other than DM, mean age 56, 73.8% male	T1DM, T2DM	42	0	No control	None	Aqueous	Suspension bead array	IL-6, VEGF

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Klaassen et al. 2019	United Kingdom	A proportion of patients were pre-treated with either bevacizumab ($n = 11$) or aflibercept ($n = 25$)	Not specified	77	53	Macular hole	Intravitreal bevacizumab, aflibercept	Vitreous	Not specified	VEGF-A, PlGF, GDNF, IL-1β, IGFBP-1, FTL-1, TNF-α
Li et al. 2019	Not specified	No patient details provided	T2DM	NA	NA	Nondiabetic	None	Vitreous	Human Cytokine Array	IL-1ra, SDF-1, IL-6, IL-8, CXCL11, MIF, MCP-1, Serpin E1, ICAM-1, GRO-1, IP-10,
Liu et al. 2019a	China	Inclusion criteria of repeated vitreous hemorrhage, pre-retinal membrane without therapy, and fundus proliferative membrane or tractional detachment of the retina, mean age 55, 53.8% male	T2DM	50	30	Macular hole	None	Vitreous	Western Blot	VEGF
Liu et al. 2019b	Not specified	No patient details provided	Not specified	24	20	Macular hole, ERM	Intravitreal conbercept	Vitreous	Cytokine-antibody array or ELISA	VEGF-A, VEGF-B, Ang-2, CXCL12, Endostatin, FGF, IL-18, MIF, MMP-1, MMP-3, MMP-7, PDGF-DD, PlGF, IL-1β, IL-2, IL-4, IL-9, IL-12, IL-13, IL-17A, G-CSF, IFN-γ, FGF, IP-10, MCP-1, MIP-1α, PDGF-BB, MIP-1β, RANTES, TNF-α, TGF-β1, TGF-β2, CTGF
Mallmann et al. 2019	Brazil	Excluded patients with silicone oil, active uveitis, or treatments within 3 months, mean age 54.4 ± 14, 79.2% male	Not specified	24	31	Macular hole, ERM, RD, VH	None	Vitreous	Bead-based multiplex immunoassay	PEDF, SAP, PDGF-AA, PDGF-BB, VEGF, IL-6, IL-8, IL-10, TNF-α, TNF-β
Mandava et al. 2019	Not specified	Subjects were excluded if they had comorbidities of the retina, vitreous hemorrhage, recent laser treatment or anti-VEGF injections, or had previous intraocular surgery other than cataract, 40% male	T2DM	17	9	Cataract surgery	None	Vitreous	Multiplex bead immunoassay	C3, C3a, C4, C5, C5a
Nezu et al. 2019	Japan	No patient details provided	Not specified	NA	NA	Cataract surgery, macular hole, ERM, RD	None	Both	Cytometric Bead Array	IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12p70, IFN-γ, TNF-α, IP-10, MCP-1, MIP-1β, RANTES, MIG, VEGF, G-CSF, GM-CSF, bFGF, FASL, Granzyme A, Granzyme B, Angiogenin
Nisic et al. 2019	Bosnia and Herzegovina	Exclusion criteria were systemic acute/chronic inflammatory conditions, malignant neoplasms, previously performed PPV surgery, and previously intravitreal or systemic anti-VEGF therapy, 57.8% male	Not specified	25	0	No control	None	Vitreous	ELISA	VEGF
Rezzola et al. 2019	Italy	Mean age 66 ± 11, 50% male	T2DM	16	0	No control	None	Vitreous	ELISA	VEGF
Sahajpal et al. 2019	Not specified	No patient details provided	Not specified	33	12	Not specified	None	Vitreous	ELISA	VEGF

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Shimizu et al. 2019	Japan	Collected samples from eyes that had migrated silicone oil microbubbles, measured retinal thickness, mean age 46.9 ± 10.8, 56.5% male	Not specified	10	7	RD	None	Aqueous	Bead-based multiplex immunoassay	bFGF, IFN-c, IL-10, IL-12p40, IL-1b, IL-6, IL-8, MCP-1, TNF-α, VEGF
Suzuki et al. 2019	Japan	PDR group underwent surgery for non-clearing vitreous hemorrhage (VH; 11 eyes), progressive fibrovascular membrane (FVM; 10 eyes), and combined FVM with VH (8 eyes), mean age 59.3 ± 10.1, 72.4% male	T1DM, T2DM	29	0	No control	None	Vitreous	ELISA	VEGF, ORAIP, MCP-1, IL-6, IL-8
Tsubota et al. 2019	Japan	Excluded patients with intraoperative use of silicone oil, IVB injection not performed, and less than 4 weeks follow-up, age 56, range 37-82, 63.6% male	Not specified	42	0	No control	Intravitreal bevacizumab	Vitreous	ELISA	VEGF
Yokomizo et al. 2019	United States	Participants were included in the study if they had ≥50 years of well-documented type 1 diabetes at time of recruitment, mean age 79, 66.7% male	T1DM	21	12	Nondiabetic	None	Vitreous	ELISA	IL-6, VEGF
Zeng et al. 2019	China	Exclusion criteria glaucoma, uveitis, history of ocular surgery, anti-VEGF treatment, severe systemic inflammatory diseases, mean age 55.6 ± 7.6, 47.4% male	T2DM	40	20	Macular hole, preretinal membrane, RD	None	Vitreous	BioPlex Pro human chemokine panel 40-plex kit	CCL21, CXCL13, CCL27, CXCL5, CCL11, CCL24, CCL26, CX3CL1, CXCL6, GM-CSF, CXCL1, CXCL2, CCL1, IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-16, CXCL10, CXCL11, CCL2, CCL8, CCL7, CCL13, CCL22, MIF, CXCL9, CCL3, CCL15, CCL20, CCL19, CCL23, CXCL16, CXCL12, CCL25, TNF-α
Abu El-Asrar et al. 2020	Saudi Arabia	Mean age 48.9 ± 13.1, 69.4% male	IDDM, NIDDM	36	20	RD	None	Vitreous	ELISA	Galectin-1, VEGF
Balogh et al. 2020	Hungry	Exclusion criteria were previous vitreoretinal surgery, penetrating injury, uveitis, aphakia, and uncontrolled glaucoma, mean age 55 ± 9.7, 62.5% male	Not specified	8	19	ERM	None	Vitreous	Multiplex bead immunoassay	Eotaxin, CTACK, bFGF, G-CSF, GM-CSF, GRO-α, HGF, IFN-α2, IFN-γ, IL-1α, IL-1β, IL-1ra, IL-2, IL-2Rα, IL-3, IL-4, IL-5, IL -6, IL-7, IL-8, IL-9, IL-10, IL-12p40, IL-12p70, IL-13, IL-15, IL-16, IL-17, IL-18, IP-10, LIF, MCP-1, MCP-3, M-CSF, MIF, MIG, MIP-1α, MIP- 1β, β-NGF, PDGF-BB, RANTES, SCF, SDF-1α, SCGF-β, TNF-α, TNF-β, TRAIL, VEGF
Chen et al. 2020	China	Patients with other types of retinopathy, with medication interference and pregnant or breastfeeding women were excluded, mean age 65 ± 9.8, 48% male	Not specified	25	20	Cataract surgery, ERM, RD	None	Both	ELISA	Ang-2, AT-1R, VEGF

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Hong et al. 2020	China	Excluded patients with previous intraocular surgery, keratitis, uveitis, glaucoma, retinopathy, systemic diseases, and malignant tumors, mean age 60.8 ± 6.8, 18.5% male	Not specified	16	35	Cataract surgery	None	Aqueous	Cytometric bead assay	IL-8, IL-10, VEGF-A, VCAM-1, bFGF, PlGF, VEGF-B
Ishikawa et al. 2020	Japan	Patients who had undergone intraocular surgery within 6 months prior to sample collection were excluded, 66.7% male	Not specified	9	9	Cataract surgery	None	Aqueous	ELISA	PN, TNC, VEGF, TGF-β2
Keles et al. 2020	Turkey	Excluded patients with previous vitreous surgery, and those that received previous intravitreal injection of any agents or laser photocoagulation within the last 3 months, mean age 55.7 ± 10.2, 45.2% male	Not specified	31	10	Macular hole	None	Vitreous	ELISA	VEGF, SDF-1α, ANGPTL2
Kubota et al. 2020	United States	Exclusion criteria of age >85, Snellen >20/320, prior PRP, anti-VEGF within 3 months prior, intravitreal or peri-bulbar injection of a corticosteroid within 4 months, poor glycemic control, implantation of fluocinolone acetonide within 30 months, or dexamethasone within 4 months, mean age 47.4 ± 11.3, 58.3% male	T1DM, T2DM	11	NA	NA	None	Aqueous	Multiplex immunoassay	IL-1β, IL-6, IL-8, IP-10, MCP-1, TGF-β1, VEGF
Li et al. 2020	China	Exclusion criteria included type 1 diabetes, systemic and previous treatment with anti-VEGF therapy, previous ocular surgery, and NVG, mean age 56 ± 10.5, 45% male	T2DM	20	20	RD	Intravitreal conbercept	Vitreous	ELISA	VEGF
Mao et al. 2020	China	Patients with former vitrectomy, neovascularization of nondiabetic etiology, vitreous hemorrhage within 2 months, or ocular inflammation and photocoagulation within 3 months were excluded, mean age 55 ± 13, 46.2% male	Not specified	26	8	Cadaveric	None	Vitreous	ELISA	IL-1β, IL-10

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Muhiddin et al. 2020	Indonesia	Exclusion criteria were previous ocular surgery within the last 2 years, existing or a history of ocular inflammation, rubeosis iridis or neovascular glaucoma, and rhegmatogenous retinal detachment, mean age 52.3 ± 10.7, 47% male	Not specified	17	5	IOL drop	None	Vitreous	ELISA	VEGF-A, PDGF-AB
Murata et al. 2020	Japan	Mean age 58.2 ± 4.1, 58.3% male	Not specified	12	8	Macular hole, ERM	None	Vitreous	ELISA	GRO-1
Ra et al. 2020	South Korea	Exclusion criteria of diabetic macular edema, eyes with hemorrhage, anterior segment neovascularization, any prior treatment for DR, mean age 54.0 ± 9.3, 49% male	T2DM	24	0	No control	None	Aqueous	Multiplex assay	VEGF
Shahulhameed et al. 2020	India	No patient details provided	Not specified	120	120	Nondiabetic	None	Vitreous	Western blot	MMP-9, sPECAM, IL-8, IL-10, sVEGFR-1, VEGFR-2, VEGF
Shen et al. 2020	China	Han Chinese ethnicity with PDR undergoing vitrectomy for VH and/or TRD, mean age 52.88 ± 17.48, 59.4% male	T2DM	32	46	Macular hole, vitreous hemorrhage, RD	Anti-VEGF injections	Vitreous	ELISA	HMGB-1, RAGE, VEGF, IL- 1β
Song et al. 2020	China	Patients were excluded with other serious diabetic complications, a history of ocular surgery including intravitreal injections, other major systemic diseases, and previous retinal laser photocoagulation, mean age 56.2 ± 13.6, 47.5% male	T2DM	40	0	No control	None	Aqueous	Cytometric bead assay	IL-6, IL-8, IL-10, VEGF, TGF-β, VCAM- 1, ICAM-1, MCP-1
Sun et al. 2020	China	Exclusion criteria included previous ocular surgery or inflammation, rhegmatogenous RD, intraoperative capsule breaks, severe systematic disease, intravitreal anti-VEGF within 2 months, PRP, anti-inflammatory drugs including topical or systemic nonsteroidal anti-inflammatory drugs or cortical steroid within 1 month, mean age 51.9 ± 10.7, 70.6% male	Not specified	17	0	No control	None	Both	ELISA	VEGF-A, IL-8, EPO, PlGF
Suzuki et al. 2020	Japan	Patients were excluded if injection of anti-VEGF, sub-Tenon or intravitreal triamcinolone acetonide within 6 months, neovascular glaucoma, PRP or focal photocoagulation within 3 months, or aphakia, mean age 53.1 ± 13.3, 57% male	T2DM	130	0	No control	None	Vitreous	Multiplex immunoassay	IL-1β, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, Eotaxin, bFGF, G-CSF, GM-CSF, IFN-α, IFN-γ, MCP-1, MIP-1α, MIP-1β, IP-10, PDGF, RANTES, VEGF

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Ucgan et al. 2020	Turkey	Patients were excluded with a history of ocular trauma, intraocular surgery, ocular inflammatory diseases or had been receiving topical or systemic steroid treatment, mean age 61.3 ± 7.6, 38.1% male	Not specified	21	21	ERM	None	Vitreous	ELISA	INF-γ, TNF-α, MMP-2, MMP-9, APN
Urbančič et al. 2020	Slovenia	Exclusion criteria of photocoagulation within 6 months, previous vitrectomy, HbA1c > 10%, systemic inflammatory or hematologic disease, mean age 63.3 ± 11.9, 48.5% male	Not specified	33	20	Macular hole	None	Vitreous	Cytometric bead assay	IL-1β, TNF-α, MIP-1α, MIP-1β, MCP-1, IL-6, IL-8, IL-10, IL-12, VEGF
Wang et al. 2020a	China	The patients who had a chronic systemic disease such as hematological or autoimmune, dialysis, cancer, ocular disorders or previous intraocular surgery were excluded, mean age 56 ± 9, 50% male	T2DM	6	20	Macular hole, ERM	Anti-VEGF injections	Vitreous	ELISA	IL-26
Wang et al. 2020b	China	Excluded patient with prior intravitreal anti-VEGF injection, panretinal photocoagulation, cataract surgery, vitrectomy, other ocular condition such as rubeosis iris or NVG, uveitis, and infectious endophthalmitis, and trauma, mean age 54.8 ± 9.3, 66.7% male	Not specified	55	19	Cataract surgery	None	Both	ELISA	IL-1β, IL-6, IL-8, IL-12, GM-CSF, IFN-γ, MCP-1, MIP-1α, MIP-1β, TNF-α, VEGF
Wang et al. 2020c	China	Patients with non-ocular pathology such as cardiovascular diseases, intestinal inflammation, breast cancer, and pancreatic diseases, along with samples from eyes obtained during a repeat vitrectomy were excluded, mean age 61.3 ± 8.2, 34% male	Not specified	47	20	Macular hole	None	Vitreous	ELISA	Lipocalin-2, VEGF
Wu et al. 2020	China	Exclusion criteria of prior vitrectomy, rhegmatogenous RD, retinal vascular occlusion, uveitis, advanced glaucoma, complicated anterior segment surgery, lens dislocation, and trauma, mean age 50.6 ± 11.7, 70.6% male	Not specified	17	7	Macular hole, ERM	Intravitreal bevacizumab, ranibizumab, aflibercept	Both	Multiplex immunoassay	IL-6, IL-8, TNF-α, MCP-1, MIP-1β, Flt-1, PlGF, VEGF-A, VEGF-C, VEGF-D

Table 1. continued

Study	Site	Study population	Diabetes subtype	Cases	Controls	Control type	Treatment type	Sample	Method of detection	Intraocular cytokines investigated
Zhang et al. 2020a	China	Exclusion criteria were previous retinal diseases besides DR, glaucoma, eye infection and intraocular inflammation, penetrating ocular trauma, intraocular surgery within 6 months, uncontrolled diabetes or hypertension, recent myocardial infarction or cerebral vascular accident, mean age 47.8 ± 11.7, 45.8% male	T2DM	24	0	No control	Intravitreal conbercept	Aqueous	ELISA	VEGF-A, VEGF-B, PlGF
Zhang et al. 2020b	China	Exclusion criteria of systemic diseases such as renal failure or uncontrolled hypertension, dense cataract, history of ocular surgery including laser and intravitreal injection, and type 1 diabetes, mean age 69.7 ± 6.3, 60% male	T2DM	15	20	Cataract surgery	None	Aqueous	ELISA	IL-10, IL-17, IL-23, TGF-β

bias in 85% (53/62) of studies. Data collection and outcome measurement, respectively, had a low risk of bias in 81% (50/62) and 100% (62/62) of studies. An unclear risk of bias in confounding was found in most studies (85%; 53/62) as most studies did not account for non-diabetic ocular or systemic conditions that may influence intraocular cytokine concentrations. Finally, 81% (50/62) of studies had an appropriate statistical analysis. Prognostic studies were found to have an overall low risk of bias.

Main association of DME with cytokine levels

Fifty-four cytokines had sufficient data for inclusion in the meta-analysis, with results detailed in Table 2. Aqueous concentrations (standard mean difference, 95% confidence interval, and p value) of IL-1β (5.76, 2.45–9.07, $p = 0.0006$), IL-6 (2.69, 1.34–4.03, $p < 0.0001$), IL-8 (2.77, 1.11–4.43, $p = 0.001$), MCP-1 (1.80, 0.72–2.88, $p = 0.001$), TNF-α (9.74, 5.01 to 14.47, $p < 0.0001$), and VEGF (2.31, 1.61–3.00, $p < 0.00001$) were significantly higher in patients with PDR when compared to healthy nondiabetic controls. For vitreous cytokines, concentrations of IL-2 (0.61, 0.18 to 1.04, $p = 0.006$), IL-4 (1.07, 0.30–1.84, $p = 0.007$), IL-6 (1.72, 1.30–2.13, $p < 0.00001$), IL-8 (1.78, 1.16–2.39, $p < 0.00001$), angiopoietin-2 (1.46, 0.93–1.98, $p < 0.00001$), eotaxin (0.99, 0.36–1.63, $p = 0.002$), erythropoietin (1.37, 0.81–1.93, $p < 0.00001$), GM-CSF (0.72, 0.34–1.10, $p = 0.0002$), GRO (1.40, 0.49–2.32, $p = 0.003$), HMGB-1 (0.86, 0.62–1.10, $p < 0.00001$), IFN-γ (0.75, 0.33–1.17, $p = 0.0004$), IGF (0.48, 0.17–0.80, $p = 0.003$), IP-10 (1.53, 0.87–2.20, $P < 0.00001$), MCP-1 (2.53, 1.76–3.30, $p < 0.00001$), MIP-1 (1.09, 0.28–1.91, $p = 0.009$), MMP-9 (0.92, 0.32–1.52, $p = 0.003$), PDGF-AA (1.28, 0.77–1.78, $p < 0.00001$), PlGF (1.33, 0.80–1.87, $p < 0.00001$), sCD40L (1.15, 0.30–2.01, $p = 0.008$), SDF-1 (1.60, 0.79–2.41, $p = 0.0001$), sICAM-1 (1.40, 0.73–2.07, $p < 0.0001$), sVEGFR (2.40, 0.92–3.89, $p = 0.002$), TIMP (0.73, 0.34–1.13, $p = 0.0003$), TNF-α (1.05, 0.34–1.77, $p = 0.004$), and VEGF (1.96, 1.69–2.23, $p < 0.00001$) were significantly elevated in subjects with PDR as compared to healthy controls. For all other cytokines intraocular concentrations were not significantly different between PDR and controls, did not pass the sensitivity analysis, or had insufficient data for inclusion in the meta-analysis.

Supplementary Table S3 shows the known associations of intraocular cytokines with PDR from the previous studies identified in the systematic review and contrasts those with the results of this meta-analysis. Of the 31 aqueous and vitreous cytokines for which we found a significant elevation in cytokine concentration in PDR versus controls, previous studies had found them to be either not significantly different or even reduced in PDR versus controls in 17% (120/700) of the cases. Forest plots for each of the analysed cytokines are available in Supplementary Fig. S3, and funnel plots for each cytokine that had at least five data points are available in Supplementary Fig. S4.

Some studies included patients that had received previous treatment for PDR, such as a laser photocoagulation or intravitreal anti-VEGF. To determine if the results of the meta-analysis was influenced by patient treatment status, two subgroup analyses were performed (Supplementary Fig. S5). When including only studies with patients that had no treatments for at least 3 months prior to study enrolment, the effect sizes for aqueous cytokines was 5.76 for IL-1β (2.45–9.07, $p = 0.0006$), 3.56 for IL-6 (2.03 to 5.09, $p < 0.00001$), 5.58 for IL-8 (2.97 to 8.19, $p < 0.0001$), 2.40 for MCP-1 (0.68–4.12, $p = 0.006$), 9.74 for TNF-α (5.01 to 14.47, $p < 0.0001$), and 2.25 for VEGF (1.54–2.97, $p < 0.00001$). Similarly, for vitreous cytokines the effect size was 1.48 for IL-6 (0.75–2.21, $p < 0.0001$), 1.37 for IL-8 (0.25–2.48, $p = 0.02$), 1.16 for IL-10 (0.44–1.89, $p = 0.002$), 1.20 for IFN-γ (0.47–1.94, $p < 0.0001$), 3.29 for MCP-1 (0.87–5.72, $p = 0.008$), −2.29 for PEDF (−3.87 to −0.70, $p = 0.005$), 0.91 for TNF-α (0.36–1.47, $p = 0.001$), and 3.11 for VEGF (2.29 to 3.93).

When including only studies with patients that had no previous treatments the effect size for aqueous VEGF was 3.08 (2.25–3.90, $p < 0.00001$), vitreous PEDF was −2.89 (−4.41 to −1.37, $p = 0.0002$),

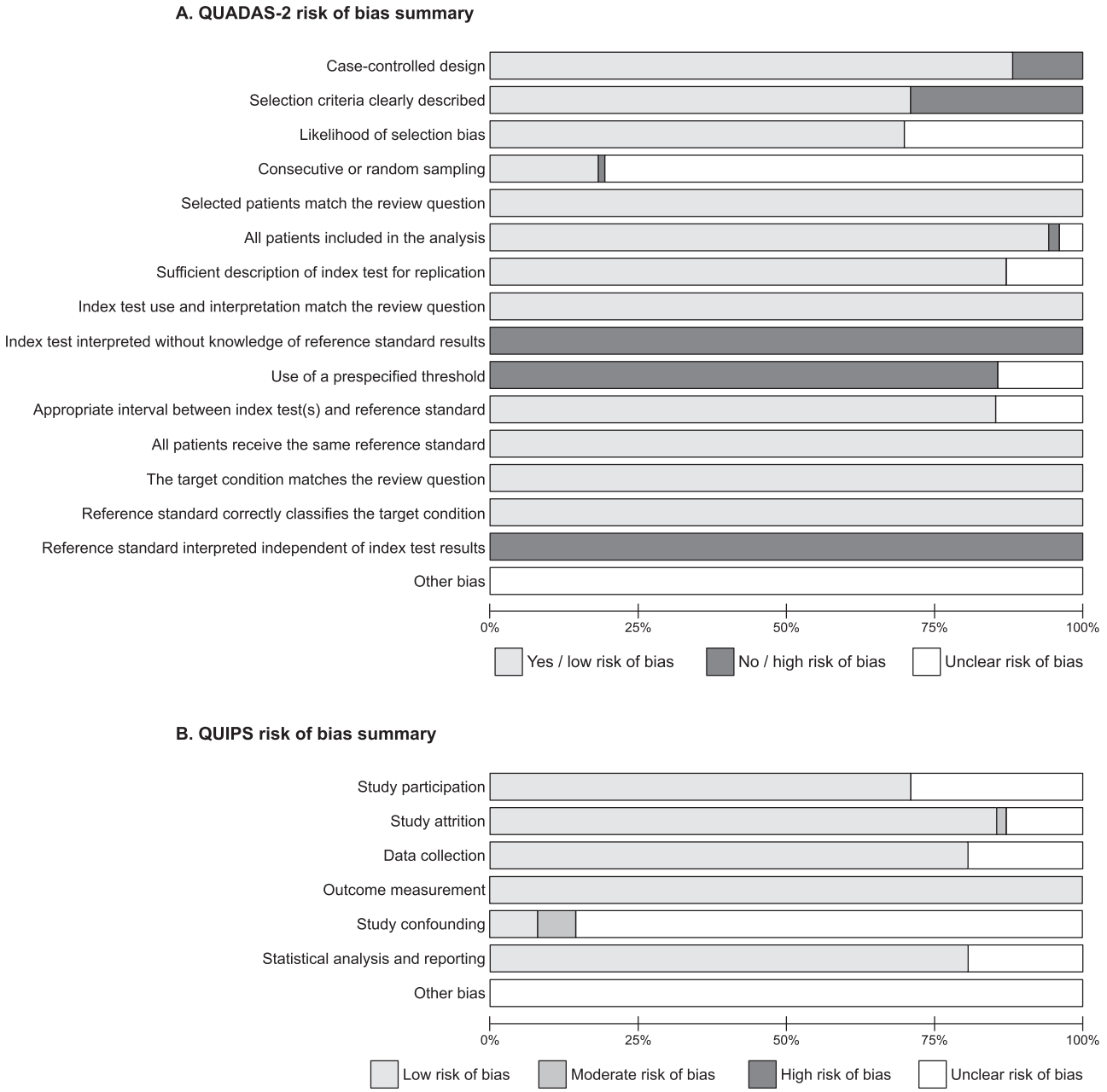

Fig. 2 Summary of quality assurance data.

and vitreous VEGF was 3.71 (2.90–4.51, $p < 0.00001$). All other cytokines failed the sensitivity analysis.

DISCUSSION

Panretinal photocoagulation has been a longstanding treatment for PDR. However, this treatment can restrict the visual field, reduce visual acuity at night, and has the potential to worsen macular oedema [352, 353]. The efficacy of intravitreal ranibizumab, an anti-VEGF agent, was compared to panretinal photocoagulation in DRCR Network Protocol S, a randomized trial of 394 eyes. This study found that ranibizumab was non-inferior to panretinal photocoagulation in terms of mean change in visual acuity and the proportion of eyes without neovascularization [354]. In both groups, however, at two years more than 40% of participants had active neovascularization on fundus photography and 2–3% had developed neovascular glaucoma. This suggests that proinflammatory or proangiogenic cytokines in addition to VEGF are likely involved in the disease process and may therefore be appropriate treatment targets.

Since 1992 there have been 341 studies on the association of intraocular fluid cytokines with PDR, with the vast majority being published in the last decade. Interpretation of this wealth of data has been complicated by inconsistencies in which cytokines may be involved in disease pathogenesis, with some studies even finding no difference in VEGF concentrations between patient with PDR and controls (for example Nishiguchi et al. 2013 [218]; Semeraro et al. 2014 [257]). Previous meta-analyses were highly selective in the cytokines investigated or did not address PDR specifically and looked at a relatively small number of studies [355, 356]. We therefore attempted to undertake a more comprehensive systematic review and meta-analysis on intraocular cytokines in PDR. This work summarizes 10379 eyes with PDR and 6269 eyes from healthy controls.

Table 2. Summary of the outcomes and description of the role in vivo of each cytokine in the meta-analysis.

Cytokine	Role in vivo	Sample type	I^2 (%)*	Sensitivity analysis	Overall effect p-value	Standard mean difference [95% confidence interval]†
IL-1β	Proinflammatory, fibroblast proliferation, macrophage migration, pyrogen	Aqueous	94; high	Passed	0.0006	5.76 [2.45 to 9.07]; large
		Vitreous	92; high	Failed	0.01	0.98 [0.21 to 1.75]; large
IL-1ra	Inhibitor of the proinflammatory IL-1β, role in treatment of autoimmune conditions	Vitreous	57; low	Passed‡	0.83	0.08 [−0.65 to 0.81]; very small
IL-2	Proliferation and differentiation of T lymphocytes, includes various interleukins, interferons and TNF	Vitreous	41; low	Passed	0.006	0.61 [0.18 to 1.04]; small
IL-4	Stimulation and differentiation of B and T cells, anti-apoptotic	Vitreous	90; high	Passed	0.007	1.07 [0.30 to 1.84]; large
IL-5	Contributes to eosinophil migration, tissue localization and function, and blocks their apoptosis	Vitreous	85; high	Failed	0.05	1.47 [0.01 to 2.94]; large
IL-6	Proinflammatory, B cell proliferation, neutrophil migration, pyrogen	Aqueous	94; high	Passed	<0.0001	2.69 [1.34 to 4.03]; large
		Vitreous	92; high	Passed	<0.00001	1.72 [1.30 to 2.13]; large
IL-7	Stimulates proliferation of lymphoid cells	Vitreous	70; medium	Failed	0.03	0.92 [0.07 to 1.77]; medium
IL-8	Granulocyte chemotaxis, phagocytosis, angiogenesis	Aqueous	95; high	Passed	0.001	2.77 [1.11 to 4.43]; large
		Vitreous	95; high	Passed	<0.00001	1.78 [1.16 to 2.39]; large
IL-10	Mast cell activity, immunoregulation and anti-inflammatory, inhibitor of IL-1, IL-2, IL-3, IL-6, IL-10 itself, IL-12, IL-18, GM-CSF, TNF-α and IFN-γ	Aqueous	96; high	Failed	0.38	−1.08 [−3.48 to 1.32]; large
		Vitreous	98; high	Failed	0.26	0.99 [−0.71 to 2.68]; large
IL-12	Stimulation and maintenance of Th1 cellular immune responses, increasing NK cell cytotoxicity via stimulating TNF-α and IFN-γ production, anti-angiogenic	Vitreous	35; low	Failed	0.002	0.73 [0.27 to 1.18]; medium
IL-13	Same α-helix superfamily as IL-4, B cell and monocyte isotype switching, inhibition of Th1, associated with allergic inflammation	Vitreous	97; high	Passed‡	0.28	1.27 [-1.04 to 3.58]; large
IL-17	Proinflammatory, links T cell activation to neutrophil mobilization and activation, induces expression of IL-6 and G-CSF	Aqueous	96; high	Failed	0.008	23.65 [6.21 to 41.09]; large
		Vitreous	94; high	Failed	0.03	1.20 [0.10 to 2.30]; large
IL-18	Proinflammatory, induction of IFN, IL-4, IL-10, IL-13 production, augments T and NK cell maturation and cytotoxicity, role in ICAM-1 and VCAM-1 adhesion, host microbial defense	Vitreous	98; high	Failed	0.005	4.67 [1.44 to 7.90]; large
IL-22	Role in wound healing and cell proliferation, antimicrobial	Vitreous	93; high	Failed	0.05	1.38 [0.00 to 2.76]; large
Ang-1	Binds to and phosphorylates the Tie2 receptor, leading to downstream signaling that promotes cell survival and vascular stability	Vitreous	0; very low	Failed	0.04	0.34 [0.01 to 0.67]; small
Ang-2	Interacts with endothelium, contributes to vascular destabilization and sensitizing blood vessels to the effects of VEGF-A	Vitreous	76; high	Passed	<0.00001	1.46 [0.93 to 1.98]; large
b-FGF	Binds heparin and possesses mitogenic and angiogenic activity	Vitreous	82; high	Passed‡	0.22	0.39 [−0.23 to 1.02]; small
Eotaxin	Eosinophil chemotaxis, may have a role on T cell chemotaxis	Vitreous	59; medium	Passed	0.002	0.99 [0.36 to 1.63]; medium
EPO	Essential role in erythropoiesis, may influence on vasoconstriction, angiogenesis, apoptosis	Vitreous	82; high	Passed	<0.00001	1.37 [0.81 to 1.93]; large

Table 2. continued

Cytokine	Role in vivo	Sample type	I^2 (%)*	Sensitivity analysis	Overall effect p-value	Standard mean difference [95% confidence interval]†
G-CSF	Proliferation, differentiation and function of granulocytes such as neutrophils, induction of hematopoietic stem cells, neurogenesis	Vitreous	67; medium	Passed‡	0.09	0.71 [−0.11 to 1.52]; medium
GM-CSF	Proliferation, differentiation and function of granulocytes and monocytes, role in embryonic development	Vitreous	0; very low	Passed	0.0002	0.72 [0.34 to 1.10]; small
GRO	Proinflammatory, role in wound healing and tumorigenesis	Vitreous	80; high	Passed	0.003	1.40 [0.49 to 2.32]; large
HGF	Regulates cell growth, cell motility, and morphogenesis through role in the tyrosine kinase signaling cascade	Vitreous	81; high	Failed	0.01	1.17 [0.26 to 2.07]; large
HMGB-1	Promotes the pathogenesis of inflammatory and autoimmune diseases once it is in an extracellular location through toll-like receptor binding and activating macrophage cytokine release	Vitreous	15; very low	Passed	<0.00001	0.86 [0.62 to 1.10]; large
IFN-γ	Role in innate and adaptive immunity, actives macrophages, implicated in autoinflammatory conditions	Vitreous	73; medium	Passed	0.0004	0.75 [0.33 to 1.17]; medium
IGF	Role in cell proliferation and inhibition of apoptosis	Vitreous	0; very low	Passed	0.003	0.48 [0.17 to 0.80]; small
IP-10	Secreted in response to IFN-γ, role in angiogenesis, chemoattraction, and T cell adhesion	Vitreous	90; high	Passed	<0.00001	1.53 [0.87 to 2.20]; large
MCP-1	Inflammation, migration of monocytes, dendritic cells, and NK cells	Aqueous	90; high	Passed	0.001	1.80 [0.72 to 2.88]; large
		Vitreous	96; high	Passed	<0.00001	2.53 [1.76 to 3.30]; large
MCP-3	Chemoattraction, diapedesis, and extravasation of various leukocytes	Vitreous	97; high	Failed	0.84	-0.21 [-2.25 to 1.84]; small
MIP-1	Involved in acute inflammation with recruitment and activation of leukocytes, chemoattractant for NK cells and monocytes	Vitreous	85; high	Passed	0.009	1.09 [0.28 to 1.91]; large
MMP-9	Breakdown of extracellular matrix, regulation of neutrophil migration, angiogenesis, and neovascularization	Vitreous	72; medium	Passed	0.003	0.92 [0.32 to 1.52]; large
PDGF-AA	A subset of PDGF; angiogenesis, cell migration, mitogenesis, synthesis of extracellular matrix, chemotaxis of neutrophils, monocytes, fibroblasts	Vitreous	0; very low	Passed	<0.00001	1.28 [0.77 to 1.78]; large
PDGF-BB	Angiogenesis, cell migration, mitogenesis, synthesis of extracellular matrix, chemotaxis of neutrophils, monocytes, and fibroblasts	Vitreous	82; high	Failed	0.50	0.39 [−0.75 to 1.53]; small
PEDF	Anti-angiogenic, apoptosis of endothelial cells, anti-tumor activity	Vitreous	97; high	Failed	0.06	−1.18 [−2.39 to 0.04]; large
PlGF	Member of the VEGF family, role in plaque inflammation, angiogenesis, and vasculogenesis	Aqueous	91; high	Failed	0.21	1.20 [-0.70 to 3.11]; large
		Vitreous	35; low	Passed	<0.00001	1.33 [0.80 to 1.87]; large
sCD40L	Part of the TNF superfamily, release of inflammatory mediators, roles in MMP activity and coagulation	Vitreous	90; high	Passed	0.008	1.15 [0.30 to 2.01]; large
SDF-1	Immune surveillance, inflammatory response, tissue homeostasis, and angiogenesis through recruiting endothelial progenitor cells	Vitreous	64; medium	Passed	0.0001	1.60 [0.79 to 2.41]; large
sICAM-1	Leukocyte adhesion and migration across endothelium, role in angiogenesis	Vitreous	84; high	Passed	<0.0001	1.40 [0.73 to 2.07]; large
sVAP-1	Mediates tissue-selective lymphocyte adhesion	Vitreous	98; high	Failed	0.05	5.58 [0.07 to 11.09]; large
sVCAM-1	Lymphocyte, monocytes, eosinophil, and basophil adhesion to vascular endothelium	Vitreous	27; low	Failed	0.01	0.53 [0.10 to 0.95]; medium

Table 2. continued

Cytokine	Role in vivo	Sample type	I^2 (%)*	Sensitivity analysis	Overall effect p-value	Standard mean difference [95% confidence interval]†
sVEGFR	Receptor for VEGF	Vitreous	98; high	Passed	0.002	2.40 [0.92 to 3.89]; large
TGF-β	Role in growth, proliferation, differentiation, and apoptosis of numerous cell types	Vitreous	61; medium	Failed	0.002	0.94 [0.35 to 1.54]; large
TIMP	Inhibitory role in MMP regulation	Vitreous	71; medium	Passed	0.0003	0.73 [0.34 to 1.13]; medium
TNF-α	Proinflammatory, role in cell differentiation, proliferation, and signaling of cell apoptosis	Aqueous	97; high	Passed	<0.0001	9.74 [5.01 to 14.47]; large
		Vitreous	94; high	Passed	0.004	1.05 [0.34 to 1.77]; large
VEGF	Vascular permeability and vasodilation, angiogenesis, chemoattractant for macrophages and monocytes	Aqueous	91; high	Passed	<0.00001	2.31 [1.61 to 3.00]; large
		Vitreous	92; high	Passed	<0.00001	1.96 [1.69 to 2.23]; large

* I^2: statistic denoting level of study heterogeneity, where <25 is very low, 25-49 is low, 50–74 is medium, and ≥75 is high.
† Standard mean difference, where an absolute value of <0.20 is very small, 0.20–0.49 is small, 0.50–0.79 is medium, and ≥0.80 is large.
‡ *p* value remains ≥0.05.

Previous studies have identified a correlation between aqueous and vitreous cytokine concentrations in diabetic retinopathy [324], and one might expect similar cytokine profiles in the aqueous and vitreous samples. In the end stage of severe retinal ischemic disease proinflammatory and proangiogenic cytokines can migrate from the posterior to anterior segment of the eye and promote new vessel formation on the iris surface or anterior chamber angle, leading to neovascular glaucoma [161, 275]. Over eighty percent (279/341) of the included studies utilized vitreous humour samples alone, which is appropriate for investigating PDR pathogenesis due to the proximity between the vitreous and the retina. However, this resulted in many aqueous cytokines having insufficient data for inclusion in the meta-analysis. Given the relative ease of aqueous paracentesis, it would be beneficial for future studies to collect both aqueous and vitreous humour samples to further elucidate the relationship between posterior and anterior disease processes.

This study found significant elevation of aqueous IL-1β, IL-6, IL-8, IP-10, MCP-1, TNF-α, and VEGF, and vitreous IL-4, IL-6, IL-8, IL-12, angiopoietin-2, eotaxin, erythropoietin, GRO, HMGB-1, IFN-γ, IGF, IP-10, MCP-1, MIP-1, MMP-9, PDGF-AA, PlGF, sCD40L, SDF-1, sICAM-1, sVEGFR, TIMP, TNF-α, and VEGF. Most of the cytokines significantly associated with PDR had a medium (0.50–0.79) to large (≥0.80) effect size and none were sensitive to the result of any one study. Many of these molecules are known to have an important proinflammatory and proangiogenic role, and for some there may be a synergistic or antagonistic affects amongst cytokines. Angiopoietin-2 influences blood-retinal barrier stabilization and vessel remodelling through mediation of Tie-2 phosphorylation and is elevated in the retina of diabetic patients with chronic hyperglycaemia [357, 358]. IFN-γ is a key participant in inflammation in diabetic retinopathy through the breakdown of the blood-retina barrier and upregulation of other proangiogenic cytokines [359]. This also induces the release of IP-10, another CXC chemokine that in turn prevents neovascularization and inhibits IL-8-induced chemotaxis [86, 360]. PDGF is a ubiquitous growth factor produced in the retina by the retinal pigment epithelium, astrocytes, and ganglion cells, and directly contributes to neovascularization and fibrovascular proliferation in PDR [361, 362]. PlGF, a member of the VEGF family, is not required for physiologic angiogenesis but does play a role under pathological conditions where levels correlate with PDR activity [133]. This cytokine is a target of aflibercept and concentrations may also decrease following conbercept injection [350]. TNF-α and sCD40-L, which is a member of the TNF superfamily, promote angiogenesis and may induce the expression of VEGF in vivo [169, 363].

The number of elevated cytokines in PDR is much greater than that seen in previous work on retinal vein occlusion [364], neovascular age-related macular degeneration [365], and diabetic macular oedema [7], and in our companion article on cytokines in NPDR. This is reflective of the complexity of PDR pathogenesis and the advanced disease state, where dysregulation of several biochemical and molecular signalling pathways is driven by oxidative stresses [366]. In the NPDR meta-analysis it was found that aqueous IL-6, IL-17, and VEGF as well as vitreous VEGF were elevated when compared to controls, all with large effect sizes. Apart from IL-17, which failed the sensitivity analysis, similar results were obtained for PDR. In addition, aqueous IL-1β, IL-8, and TNF-α were elevated in NPDR versus controls but failed sensitivity analysis, making their significance inconclusive. Given that these cytokines were elevated in PDR, it suggests that the importance of their role in the nonproliferative form of DR may be better elucidated with additional studies.

When including only studies where all participants were without treatment for their PDR in the preceding 3 months, aqueous IL-1β, IL-6, IL-8, MCP-1, TNF-α, and VEGF and vitreous IL-6, IL-8, IL-10, IFN-γ, MCP-1, TNF-α, and VEGF were found to be significantly elevated and, in most cases, had larger effect size than found in the primary analysis. Furthermore, when using only data from treatment-naive patients only aqueous and vitreous VEGF was significantly elevated in PDR, with other cytokines having an insufficient number of studies or a failed sensitivity analysis. Due to notable heterogeneity in treatment type, duration, and the use of combination therapy, we were not able to stratify patients by the type of prior treatment. Our analysis was further limited as some studies did not provide sufficient detail on the nature of prior treatments. It would be interesting to investigate the influence of specific prior treatments on the cytokine milieu since these may have different mechanisms and durations of action, allowing for a better understanding of the post-treatment cytokine profile.

In both the treatment-free for 3 months and treatment naïve subgroups PEDF was significantly lower in PDR than in controls, with an effect size of -2.29 (-3.87 to -0.70) in those without treatment for 3 months and -2.89 (-4.41 to -1.37) for those without

any prior treatments. PEDF can counteract VEFG-induced vascular permeability and inhibit retinal neovascularization [362, 367, 368], acting as an inhibitor of VEGF function through its action on the VEGF receptor [369]. It is disruptions to the balance of proangiogenic and antiangiogenic cytokines because of chronic hyperglycaemia in diabetes that leads to proliferative retinopathy and its sequelae [53, 370]. It therefore fits mechanistically that patients with more active neovascularization would have lower levels of PEDF. While angiogenic stimuli such as VEGF are required for PDR to occur, pathology can only develop when the 'break' of negative regulators such as PEDF fail [371].

Of the 31 aqueous and vitreous cytokines for which we found a significant elevation, 17% (120/700) of previous investigations had found them to either be not significantly different or reduced in PDR when compared to controls (Table S3). There are several possible reasons for this inconsistency in the literature. There is a variable nature to an individual's cytokine profile. While there is little data available on longitudinal intraocular cytokine concentrations, work on plasma cytokines indicates that levels are sensitive to the duration of diabetes [372], acute episodes of hyperglycaemia [373], and systemic factors such as hypertension [374] and dyslipidaemia [375]. Furthermore, the 'healthy' control groups often contained patients of different ethnicity and with either systemic or ocular conditions such as macular hole or epiretinal membrane that may influence cytokine concentrations [376, 377]. As studies generally had small sample sizes, with a median of 27 cases and 20 controls, they may be particularly susceptible to these influences. Future work using large ocular fluid biobanks may provide a normative database that identify genetic, temporal, and comorbid variations in the cytokine profile, and upon which changes specifically due to PDR can be further elucidated. Over 70% of studies utilized enzyme linked immunosorbent assays for cytokine quantification, with more recent studies being predominantly based on multiplex analysis. There remains both intra-assay and inter-assay variability due to differences in sample collection, handling, and storage as well as the types of buffers and antibodies used. It is unclear to what extent these impact reported cytokine concentrations, and if a correction factor should be applied when comparing data from different assay types.

CONCLUSIONS

Previous studies have shown conflicting associations for most cytokines assessed in PDR. This meta-analysis demonstrated elevated aqueous concentrations of IL-1β, IL-6, IL-8, MCP-1, TNF-α, and VEGF, and vitreous concentrations of IL-2, IL-4, IL-6, IL-8, angiopoietin-2, eotaxin, erythropoietin, GM-CSF, GRO, HMGB-1, IFN-γ, IGF, IP-10, MCP-1, MIP-1, MMP-9, PDGF-AA, PlGF, sCD40L, SDF-1, sICAM-1, sVEGFR, TIMP, TNF-α, and VEGF in patients with PDR.

When assessing patients without recent treatment, levels of the anti-angiogenic cytokine PEDF were low. This work identifies a number of candidate cytokines other than VEGF that are implicated in PDR and adds clarity to the large body of literature. These findings suggest potential biomarkers of PDR development and severity and point to potential therapeutic targets.

Supplemental information is available at Eye's website.

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AUTHOR CONTRIBUTIONS

RHM (or Mason) had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. RHM provided study concept. SAM designed the study. All authors acquired the data. RHM, SAM, and RHM analysed or interpreted the data. RHM and SAM conducted the statistical analysis. RHM, SAM, GLL and RHM drafted the manuscript. All authors critically revised the manuscript for important intellectual content. RHM supervised the study.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL APPROVAL

This systematic review and meta-analysis did not involve any participants, and thus ethical approval was not necessary.

INFORMED CONSENT

There were no direct participants in our study, and thus informed consent was not necessary.

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