The Vitreous, the Retinal Interface in Ocular Health and Disease

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Key Words

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Abstract

The vitreous is a complex structure whose composition and appearance change with age. Anomalous adhesions between the posterior vitreous face and the retinal surface are the cause of numerous vitreoretinal complications, while the presence of an intact posterior hyaloid provides a scaffold for vascular growth and anteroposterior traction. This review summarizes what is known about the biochemistry of the vitreous, the process of posterior vitreous detachment (PVD) development, and the available clinical approaches to examining the vitreous and its interface. A pooled analysis of studies looking at the presence of a complete, partial or absent PVD in a number of macular and retinal diseases allows us to establish odds ratios for these various states. From this emerge both protective and disease-associated states in conditions such as proliferative diabetic retinopathy, macular edema, and age-related macular degeneration. With the emergence of pharmacological means to separate the posterior hyaloid, a better understanding of the possible role of the vitreous in tractional syndromes is required.

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Introduction

Within the eye, no other component occupies as much space as the vitreous; eye movements induce incessant stress forces, and with age, its composition and structure change. Its role in the physiology and pathobiology of the eye is being increasingly appreciated, but its study is complicated due to its invisible nature. Vitreous liquefaction and posterior vitreous separation have particularly important consequences for ocular health and disease. Modifying the intraocular structure by ever evolving therapeutic modalities has reduced the incidence of blindness. While in the future, the vitreous will be modified by pharmacological means, their success will depend on an adequate understanding of its physiological and pathological role in vitreoretinal disorders.

Biochemistry and Physiology of the Vitreous

Vitreous Composition

The vitreous is the largest structure within the eye occupying about 80% of the ocular volume [1]. It is a highly hydrated transparent extracellular matrix containing 98–99% water [2]. Its gel structure is maintained by a 3-dimensional network of randomly spaced, nonbranching collagen fibrils, held apart by hyaluronan (HA) and other macromolecules. The collagen concentration is low, approximately 300 µg/ml [3], with type II collagen being the

main component [4, 5]. The distribution within the eye is not uniform, the highest concentration being present at the vitreous base followed by the posterior vitreous cortex, and the vitreous core [3]. This network of collagen fibers provides the vitreous with mechanical strength, allowing it to sustain impacts, and transmit tractional forces to the retinal surface [2].

HA is the major glycosaminoglycan present in the mammalian vitreous [6]. It serves to inflate and stabilize the collagen network [7, 8]. The adult human vitreous has a HA concentration ranging between 65 and 400 µg/ml with the highest concentration present in the posterior cortical vitreous [7]. HA-collagen interactions insure proper hydration and spacing, thus decreasing light scattering and enhancing transparency. It also provides the vitreous with its viscoelastic properties [6, 8, 9]. Other molecules such as opticin are also present in the human vitreous and help to further stabilize its structure [7, 9].

The vitreous is acellular except for a sparse population of hyalocytes, oval to spindle-shaped mononuclear cells measuring 10–15 µm in diameter. These phagocytic cells are mostly concentrated in the vitreous base and adjacent to the posterior pole [6, 7, 10, 11]. They are involved in the synthesis of vitreous components such as collagen fibrils, HA and other macromolecules, and have been implicated in a number of pathological eye conditions [12].

Vitreoretinal Interface

The vitreous is surrounded by the lens, ciliary body anteriorly and by the retina. The interface between the vitreous and its surroundings is composed of vitreous cortical fibrils and the basal laminae of the adjacent tissues [13]. The internal limiting lamina (ILL) of the retina formed mainly by the basal lamina of Müller cells [14] is composed of collagen types I and IV, proteoglycans, fibronectin, and laminin [15–18]. These and other components of the extracellular matrix are the targets of pharmacological posterior vitreous detachment (PVD) with agents such as plasmin, microplasmin, and dispase. They may eventually replace the conventional surgical induction of PVD [19–25]. The ILL varies in thickness and composition. At the vitreous base, it measures about 50 nm and progressively thickens as one follows it posteriorly, measuring 300 nm at the equator, 1,890 nm at the posterior pole. It thins again over the fovea to about 10–20 nm [13, 23, 26]. Over the optic nerve, the inner limiting membrane is 50 nm thick and is formed by the basal lamina of the astroglia present on the surface of the nerve (ILL

of Elschnig). At the most central part of the optic nerve, the membrane thins to 20 nm and follows the irregularities of the underlying cells. This structure is known as the central meniscus of Kuhnt and is composed of only glycosaminoglycans [13, 27].

Firm vitreoretinal attachments are observed in areas with thin ILL as occurs at the vitreous base, optic disk, fovea, and over the major retinal blood vessels [28]. At the vitreous base, collagen fibrils are coarse, numerous, and run perpendicularly to the ILL; in the equatorial and posterior regions, the fibrils are finer and almost parallel to the retinal surface [29]. Attachment plaques between Müller cells and the ILL are present everywhere except in the macula [13, 28, 30].

Aging Vitreous and Its Consequences

The aging vitreous both liquefies and aggregates. Synchysis, the process of vitreous gel liquefaction, first appears at around 4 years of age. The process begins in midlife and in most cases progresses slowly into late age [31, 32]. Aggregation (syneresis) is a consequence of changes in the chemical or conformational state of HA and its interaction with collagen. These alterations lead to increased fibril concentration in the residual gel, associated with a decreased concentration and ultimate absence of fibrils in adjacent areas resulting in liquefaction [33, 34]. As liquefaction appears in the central vitreous and overlying the macula, incident light weakens collagen through the production of free radicals [35–38], and modifies the concentrations in glycosaminoglycans and chondroitin sulfate [39]. Artificially inducing such changes leads to vitreous liquefaction and separation of the posterior hyaloid [22, 40, 41].

Posterior Vitreous Detachment

PVD refers to the separation of the posterior vitreous cortex from the ILL of the retina. Two clinical entities may be confused with, but should be distinguished from, a true PVD [42]. First, vitreoschisis consists in a split of the posterior vitreous cortex into two independent layers – an anterior layer moving forward with the bulk of the vitreous gel, and a posterior layer remaining attached to the ILL. It is often observed in high myopia and connective tissue disorders or in other situations where the vitreous is rapidly or extensively liquefied (proliferative diabetic retinopathy, vitreous hemorrhage) where it may contribute to the disease process [43–48]. The second entity occurs when the vitreous separates together with the

ILL from the retinal surface. This most commonly occurs in younger individuals in whom significant tractional forces were exerted at the retinal surface as in trauma due to blunt ocular injuries or in the setting of inner retinal ischemia. Under these extreme circumstances, Müller cells have weakened inner segments, which can separate from the retinal surface if sufficient shearing forces are applied [49].

Most PVDs evolve from an interplay between vitreous synchysis and weakening of the adhesions between the posterior vitreous cortex and the ILL. Once liquefied, premacular vitreous can find its way to the retrohyaloid space through either the central meniscus of Kuhnt, or through a break in the thinned posterior vitreous cortex overlying the macula. With successive ocular saccades, further fluid shifts dissect a plane through the preretinal space leading eventually to a complete PVD (CPVD) [50–52]. As a consequence of these fluid movements, the remaining gel undergoes collapse and moves forward [35, 53]. In a study on 61 postmortem human eyes, Larsson and Österlin [53] found that the degree of vitreous liquefaction increased with the degree of PVD: no PVD (NPVD), partial PVD (PPVD), and complete PVD (CPVD) corresponded to 10, 23 and 42% of gel liquefaction.

Floater and photopsias are the most common symptoms reported with the abrupt onset of a PVD [54]. Floaters are caused by aggregations of collagen fibrils, epiretinal glial tissue adherent to the posterior vitreous cortex and small dome-shaped posterior hyaloid elevations which scatter light before it reaches the retina (fig. 1). Murakami et al. [55] found a PVD in 83% of eyes following a sudden onset of floaters. The incidence is higher in patients above 50 years of age (95%). Most floaters originate from condensed vitreous material located a short distance from the retinal surface (fig. 1b) [56]. Under these conditions, incident light causes a conal shadow to form behind the floater, which is visible on the retinal surface (fig. 2). With increasing separation between the floater and the retinal surface, this shadow vanishes rendering the floater invisible. Surrounding the shadow, the penumbra, which usually blends into an uneven background, may become visible on a uniform white background. Smaller pupil sizes, as occurs with intense light will cast a conal shadow over a longer distance, allowing floaters to reappear.

Photopsias caused by vitreoretinal traction are an ominous sign of a retinal tear, particularly when associated with the appearance of multiple floaters [57–59]. Photopsias in this context are often reported as lightning

Fig. 1. Depending on their position and size, floaters are capable of casting a shadow on the retinal surface and be perceived by the OCT. **a** On the scanning laser ophthalmoscopy image, a floater is visible inferotemporal to the macula and is visible to the left of the macula on the corresponding image but is not visible within the vitreous. **b** In asteroid hyalosis only large condensation causes a shadow on the retinal surface (arrows). **c** Shallow elevations of the posterior hyaloid also cause patients to complain of shadows that are fixed in position when the eye moves.

streaks, vertical or oblique. In the first 24 h, astute observers have described them as ‘dark light flashes’ [56, 60]. As opposed to flashes from other causes, they are often better perceived in the dark, fleeting in nature, and colored [61].

Stages of PVD

Early Stages of PVD

Age-related PVD usually starts as a shallow perifoveal separation. Early on, the posterior vitreous face separates from the perifoveal area but maintains residual attachments to the fovea and the optic disk (fig. 3, panel A) [38, 62, 63]. If persistent, these perifoveal attachments pull on the fovea through dynamic tractional forces exerted during ocular saccades. Progression to a CPVD is a slow process, leaving plenty of time for such tractional forces to cause damage such as macular holes or edema. Of 31 eyes with perifoveal vitreous detachment followed prospectively, only 3 evolved to a CPVD over a 30-month period [64].

Fig. 2. Schematic diagram showing the effect of the pupil size on the conal shadow cast behind a floater onto the retinal plane. The small circles next to the retinal plane indicate the size of the shadow in relationship to the size of the floater if the retina was present in this particular plane. In the upper panel, the pupil is drawn 1.5 times larger than in the lower panel, all other scales are kept intact. The conal shadow is narrower and longer in the lower panel which allows floaters to be more visible and appear larger. It also allows floaters further distant from the retinal surface to be visualized in strong light causing a smaller pupillary opening. Adapted from Serpetopoulos [160].

Color version available online

Color version available online

Fig. 3. Schematic diagrams illustrating different stages of PVD. **A** Macular PVD. **a** PVD at the level of the macula begins in a perifoveal location. **b** The PVD extends itself to the optic nerve. **c** Further extension occurs temporally. **d** Even after the fovea has become detached, attachments around the nerve may persist for a prolonged period of time before there is complete detachment from the optic nerve. **B** PVD extension beyond the macular area. **a** PVD starts in the foveal and parafoveal area. At this stage, an attachment to the fovea is often present. **b** The detachment most often extends first in a superior direction. At this stage, the fovea may still be attached to the pos-

terior hyaloid. **c** The PVD extends further in a superotemporal and nasal direction. The foveal attachments are often gone by this stage. **d** Extension continues in an inferotemporal direction before extending further nasally (not shown). **C** CPVD. It may take on a number of different appearances depending on the etiology underlying its formation. **a** Complete vitreous detachment with collapse characterized by a sigmoidal shape posterior hyaloid. **b** CPVD without collapse which is shallowly detached and poorly motile. **c** PPVD with a taut posterior vitreous cortex. **d** PPVD with attachment at the macula. Adapted from Kakehashi et al. [67], Johnson [32] and Ito et al. [65].

Late Stages of PVD

The extension from the macula to the periphery generally follows a specific pattern. Extension first occurs to the arcades, where attachments between the posterior hyaloid and the adventitia of vessels may retain the hyaloid for a while. From there, extension progresses first upwards towards 12 h before moving temporally. Nasal and inferior quadrants are the last to witness vitreous separation [65] (fig. 3, panel B). This pattern of detachment helps explain why iatrogenic tears in macular hole surgery tend to be located inferiorly rather than in superior quadrants [66]. In these patients, PVD is often incomplete particularly with smaller holes. During surgery, a PVD is often deliberately and energetically induced leading to the formation of tears, as the vitreous retains firm adhesions to the inferior peripheral retina.

Optical Coherence Tomography and Biomicroscopic Classification of PVD

Biomicroscopically, PVD is often classified into 1 of 4 patterns based on findings in the vitreous proper and at the posterior hyaloid (fig. 3, panel C) [67]. With optical coherence tomography (OCT), a similar classification has been proposed but depends on the ability to visualize the interface. PPVDs are clearly visible, but absent PVDs or CPVDs with vitreous collapse beyond the limits of the scanning area imposed by the machine would appear the same. It is important to obtain multiple scans, preferably a stack allowing transverse imaging as this may provide additional information (see the section on clinical assessment by OCT below) [68–70]. Scanning over the optic nerve looking for residual attachments at this level is also important.

(1) A CPVD with vitreous collapse is characterized by vitreous lakes, the presence of a Weiss ring, and a large retrohyaloid space. The posterior hyaloid often has a sigmoidal shape and is highly motile. This type is commonly seen in elderly people and in high myopia.

(2) CPVD without vitreous collapse is characterized by minimal vitreous liquefaction, a clearly defined retrohyaloid space, and the presence of a Weiss ring. The posterior hyaloid is located a short distance from the retinal surface and lacks much motility. This type is characteristic of patients with uveitis or retinal vein occlusions where the increased blood components or inflammatory cells cause a separation of the posterior hyaloid without significant vitreous liquefaction.

(3) PPVD with a taut posterior hyaloid has anchoring points present to the optic disk, the vascular arcades, and/or neovascular complexes. It is typically seen in patients with proliferative diabetic retinopathy.

(4) PPVD without a taut hyaloid shows vitreomacular attachments still present through the premacular hole to the fovea, and elsewhere, particularly at the optic nerve [68, 70–72].

Epidemiology

Classical studies suggested an incidence of about 50% at the age of 50, and 65% beyond 65 years [73]. Use of OCT has shown that PVD is a much slower process requiring several decades for completion in most individuals [31, 72, 74]. In pathological states, the process will initiate itself earlier, as in myopia, where the age of onset depends on the degree of myopia [54, 75, 76]. On average emmetropes initiate their PVD around 61 years of age, while for a –5-dpt myope, it starts at 56 years, for –10 dpt at 52 years, for –20 dpt at 43 years, and for –30 dpt at 34 years [77]. A higher incidence of PVD has been observed in women, occurring also at a lower age than men, a finding that may be related to hormonally controlled changes in HA concentrations occurring around the menopause [77–80]. PVD is 7–10 times more frequent in aphakic as compared to phakic eyes [38], likely as a result of changes in the composition of the vitreous following cataract extraction. In pseudophakics, a very fluid vitreous and a PVD develop within about 18–24 months after surgery. The exact rate of change is influenced by the type of extraction, the state of the posterior capsule, and the degree of myopia [81–84].

Aberrant PVD and Its Consequences

Widespread synchysis can lead to a separation of the vitreous gel from the retinal surface without release of the vitreoretinal interface – an anomalous PVD [85]. In such cases (table 1), traction is exerted at the interface between the zone of vitreous liquefaction and vitreoretinal adherence, a phenomenon known as vitreomacular traction. If the forces exerted are sufficiently strong, they lead to the development of tears, retinal hemorrhages, retinal neovascularization, macular or lamellar holes, edema, or other deleterious effects depending on the traction's location [48, 85–87]. In addition, an anomalous PVD leaves the outer layer of the posterior vitreous cortex attached to the retina (vitreoschisis) [88]. Contraction of this layer onto the retinal surface, or its use as a scaffold, can lead to the formation of an epiretinal membrane or tangential tractional complexes as seen in high myopia (fig. 4). Excessive gel liquefaction is observed in a number of circumstances such as with inborn errors in collagen metabolism (Stickler's, Marfan's, and Ehlers-Danlos syndromes) [89, 90], intraocular inflammation [91, 92], diabetes [93], ocular trauma [94], and in high myopia [75].

Fig. 4. Vitreous liquefaction often occurs earlier than posterior vitreous separation in high myopes leading to the formation of thick posterior hyaloidal membranes which have a very elastic nature when removed surgically.

Table 1. Vitreoretinal consequences of anomalous PVD

Traction site	Retinal effect	Vitreous effect
Blood vessels	Retinal hemorrhages Enhanced retinal neovascularization	Vitreous hemorrhage
Periphery	Retinal tears/detachments Retinal tractions	White without pressure PVR
Macula	Vitreomacular traction syndrome Aggravation of macular edema from all causes	Macular holes Macular puckers PDR
Optic disk	Aggravation of NVD	

PVR = Proliferative vitreoretinopathy; PDR = proliferative diabetic retinopathy; NVD = neovascularization of the optic disk.

Clinical Assessment

Slitlamp Biomicroscopy

Several lenses have been developed to enhance the ability to see the central and posterior vitreous (table 2). Depending on the lens configuration, an erect or inverted, real or virtual image is produced. Most of these have fallen into disfavor given the availability of OCT, but they are useful to rapidly gain an understanding of the vitreous proper in 3 dimensions, particularly beyond the region visible with current imaging systems.

To optimally examine the vitreous, it is best to use a systematic approach. First, the central region is examined, identifying the presence or absence of vacuolation (synchysis), and/or a PVD. If the latter is present, the extent of detachment can be determined by following the posterior vitreous cortex peripherally. Rocking the lens, and using a large slit beam can enhance visualization of the posterior cortex. Visualization of the premacular cortex can best be done by retroillumination using reflected light from the retinal surface on an appropriately magni-

fied image. Visualization of the peripheral vitreous is accomplished by using wide-field lenses, but this is more difficult to detect and will only be clearly seen in cases where the central PVD was visible at the level of the posterior vitreous cortex.

Optical Coherence Tomography

Clinically relevant vitreomacular adhesions, macular holes, and pseudoholes have been documented by conventional time domain OCT [70, 95–98]. A posterior hyaloid membrane is seen in 57% of patients with idiopathic macular holes on OCT but is detected biomicroscopically in less than half of these patients [99–101]. Although time domain OCT can visualize the vitreomacular interface including the posterior hyaloid, information is limited by the relatively slow scan speed and poor image registration. Alternate scanning strategies combined registration with a scanning laser ophthalmoscope, the use of multidepth scanning with spectral domain OCT, or the use of broad-band light sources provide a more detailed view of the retinal surface [102–105].

Table 2. Characteristics of various lens types used to examine the vitreous and the vitreoretinal interface

Name	Lens design	Power, dpt	Field of view, degrees	Image magnification, n-fold	Image type	Working distance, mm
Hruby	planoconcave	-55	5-8	1	virtual erect	15
El Bayadi	planoconvex	+58.6	50	1.2	real inverted	18.5
60D	biconvex	+60	68	1.15	real inverted	13
90D	biconvex	+90	74	0.76	real inverted	7
Digital 1.0×	biconvex	+66	60	1	real inverted	12
Digital high mag	biconvex	+55	57	1.3	real inverted	13
Digital wide field	biconvex	+120	103	0.72	real inverted	4
Super 66	biconvex	+66	80	1	real inverted	11
Superfield	biconvex	+100	95	0.76	real inverted	7
Supervitreous	biconvex	+120	103	0.57	real inverted	4
Panfundusopic	biconvex	+85	70	0.51	real inverted	contact
Quadraspheric	concave-convex + biconvex	+120	120	0.51	real inverted	contact
HR wide field	concave-convex + biconvex	+135	160	0.5	real inverted	contact
HR Centralis	concave-convex + biconvex	+60	74	1.08	real inverted	contact
Mainster	convex	+61	60	0.92	real inverted	contact
Goldmann	planoconcave	-67	30	0.86	virtual erect	contact

Media opacities have an influence on image quality irrespective of the scanning technique. Corneal opacities or drying has substantially more effect than cataracts [106]. Vitreous opacities unless they are dense in nature, and in close proximity to the retina, have limited effect on the quality of the signal generated (fig. 1).

The OCT characteristics of vitreomacular traction are shown in figure 5. At the retinal surface, the vitreoretinal interface shows as a discrete reflective line above the nerve fiber layer with which it has either a number of discrete attachments points, or forms a broad firm attachment [103, 107, 108]. A broad insertion is more likely to be associated with macular edema or to lead to macular hole formation. Using 3-dimensional surface rendering, the number of attachment points between the posterior hyaloid and the retinal surface can be determined. These attachments are also relevant in macular pucker where more points of attachment are associated with a worse visual prognosis [102].

Ultrasound

Ultrasound has traditionally been used to determine the state of the vitreous, and to identify the presence and extent of a PVD. Strong echoes are produced by 'acoustic' interfaces found at the junctions of media with different densities and sound velocities. The greater the difference in density between two media, the more prominent the echo [109]. Contact B scan is superior to biomicroscopy and

OCT even in the absence of media opacity [110]. It is the technique of choice in cases with vitreous hemorrhage [111]. The signal can be enhanced following the injection of triamcinolone into the vitreous cavity, and might be an interesting adjunctive diagnostic technique in patients requiring surgery [112]. In a study of 94 patients to evaluate the relationship between the posterior hyaloid membrane and the retina in patients with idiopathic macular hole, a persistent attachment to the foveola with perifoveolar PVD was evident by ultrasound in 83 and 67% of patients with stage 1 and 2 holes, respectively [113]. Additionally, axial views identified a separation of the posterior hyaloid membrane from the perifoveal retina in 13 out of 13 (100%) patients with stage 1 and 2 holes, separation of the posterior hyaloid membrane from the fovea and perifoveal retina with peripapillary attachment was evident by ultrasound in 65 out of 65 (100%) patients with stage 3 hole. The advent of high-resolution OCT scans over a larger area particularly when it includes the optic nerve may well supplant the use of the ultrasound in most cases [70, 72, 114, 115].

Influence of PVD in Selected Retinal Pathologies – Meta-Analysis

The posterior hyaloid has been implicated in a number of macular diseases. Its role is mentioned in scattered case reports, small case series, and a few prospective studies. It

Fig. 5. Two- and 3-dimensional spectral OCT images of macular traction. In all images the posterior hyaloid is visible. **a** The vitreous passes through a narrow opening in the posterior hyaloid and causes persistent traction on the fovea. **b** The area of posterior

hyaloid attachment is broader. Coarse retinal ridges represent attachments of the vitreous to the retina. Finer attachments between the retina and posterior hyaloid. Fine ridges on the retinal surface in both panels are due to an epiretinal membrane.

is difficult to assess in a reliable way the risk and benefits associated with PPVD or CPVD from such varied sources.

In order to quantify the benefits of PVD, and establish odds ratios (ORs) associated with PPVD or CPVD, a systematic review of the literature was undertaken using the following methodology. A broad systematic review method was used to cover the literature between 1980 and October 2012 in Embase, Medline and Web of Science. Studies were identified in these databases using cross-references from original articles and reviews. We identified 609 articles of which 130 were reviewed in detail, allowing us to retain 56 for further analysis. Only 39 were used to produce the statistical analysis reported below.

The search strategy to identify articles used the following terms:

- Spontaneous posterior vitreous detachment
- Vitreous body detachment
- Posterior vitreous face detachment
- Posterior hyaloid face detachment
- Corpus vitreum detachment

In the current analysis, we used prospective studies, retrospective analyses of data from randomized controlled trials, observational studies, and case report studies evaluating the association between spontaneous PVD and disease course. Only English language articles were used, except for age-related macular degeneration (AMD) where due to the limited number of articles available on the subject, a German language article was also included. After excluding editorials, conference proceedings, letters, news articles, government reports, and practice guidelines, two investigators (M.d.S. and A.G.) independently screened titles and abstracts to identify potentially relevant citations. Data of eligible articles was formatted in terms of absence (NPVD), the presence of a PPVD or CPVD and its effect on prevalence, incidence or outcomes in specific ocular conditions determined based on the availability of sufficient data. CPVD was defined as a complete separation of the posterior vitreous cortex from the ILL of the retina in the posterior pole. PPVD referred to cases that were described in sufficient details by the authors as having an incomplete separation of the poste-

Table 3. State of vitreoretinal traction and the relative risk of retinal pathologies (expressed in ORs)

Vitreoretinal condition	Studies, n	Eyes studied, n	CPVD vs. NPVD	PPVD vs. NPVD	PPVD vs. CPVD
PDR vs. NPDR	5	1,239 vs. 949	0.097 (0.050–0.188)	24.1 (16.5–35.3)	186 (90–284)
PDR progression vs. none	2	104 vs. 208	0.029 (0.093–0.91)	6.2 (3.3–12)	15.2 (3.70–62.4)
RVO neovascularization vs. none	5	52 vs. 157		0.055 (0.02–0.15) ¹	
Presence of ME in DM or RVO	6	487 vs. 170	0.50 (0.27–0.93)	0.56 (0.35–0.91)	0.37 (0.20–0.71)
ME persistence or resolution after spontaneous PVD	12	213 vs. 108		0.30 (0.16–0.57) ¹	
MH late vs. early	3	112 vs. 372	21.5 (7–65)	2.6 (1.3–5.1)	0.15 (0.04–0.50)
AMD vs. age-matched controls	2	202 vs. 158	0.37 (0.21–0.67)	0.96 (0.58–1.6)	0.33 (0.16–0.88)
AMD vs. age-matched controls	4	443 vs. 349	1.62 (1.18–2.23) ²		
Wet vs. dry AMD	2	87 vs. 113	0.52 (0.29–0.92)	1.83 (1.03–3.24)	0.30 (0.15–0.58)

ORs are given with the 95% CI in parentheses. DM = Diabetes mellitus; ME = macular edema; MH = macular hole; NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; RVO = retinal vein occlusion.

¹ PPVD or CPVD are grouped together.

² Partial and none are grouped together or not differentiated.

rior hyaloid from the retinal surface. In each disease, we calculated the weighted OR over the available studies using the fixed-effects model, and tested the assumed homogeneity between studies with a Q test. The results of these analyses are given in table 3.

Influence of PVD on Retinal Neovascularization

Neovascularization on the retinal surface cannot occur without an appropriate scaffold of collagenous material. Hence, the presence of a PVD should provide relative protection in susceptible individuals, particularly if associated traction is removed. In proliferative diabetic retinopathy, 5 studies were identified for a total of 2,188 eyes, in which the state of the posterior hyaloid (CPVD, PPVD, or NPVD) was studied in terms of its association with concomitant proliferative or nonproliferative diabetic retinopathy (table 3) [116–119]. Pooled analysis of these 5 studies found that diabetic patients having CPVD indeed had a statistically significant lower prevalence of proliferative disease compared to NPVD (OR 0.1, 95% confidence interval, CI, 0.05–0.18). By opposition, patients with PPVD had a 24 times greater prevalence of proliferative disease than those with NPVD. The difference with patients who had CPVD was considerably higher at 186. The effect of PVD on progression of proliferative disease was examined in 2 studies with a minimum of 6 months of follow-up [116, 120]. Only patients with active proliferative diabetic retinopathy were included in these studies. Pooling allowed calculation of an OR for 312 eyes. Progression of proliferative diabetic retinopathy

was significantly associated with NPVD or PPVD (OR 0.3, 95% CI 0.09–0.91). PPVD had a 6 times higher rate of progression than NPVD, but a 15 times higher rate than CPVD.

Five studies were identified that looked at the association of PVD with neovascularization in vein occlusions [121–125]. Patients included in these studies had ischemic retinal vein occlusions, were followed up for a minimum of 6 months (range 6–97), and were classified based on the presence or absence of a PVD without reference to the extent of PVD. In total 209 eyes were reported. The presence of a PVD at the onset of the follow-up period significantly reduced the risk of developing neovascularization (OR 0.06, 95% CI 0.02–0.15). Of interest, Kado et al. [126] studied the effect of retinal vein occlusion on the posterior vitreous status in 26 patients and compared it with 18 normal individuals with NPVD at the initial examination (no retinal vein occlusion) over a 1-year period. They found that 58.5% of patients with a vein occlusion developed CPVD by 6 months, with 69.6% having a PVD by 12 months as compared to 25% in the control group at both 6 and 12 months of follow-up. Records of patients undergoing an optic neurotomy or arteriovenous sheath separation indicated that the vast majority of patients had an intact posterior vitreous face prior to surgery (central retinal vein occlusion 56/61 patients; branch retinal vein occlusion 35/38) [127], an incidence which according to the authors is much higher than expected from historical controls obtained by ultrasonography. Imaging using spectral-domain OCT revealed a high fre-

quency of perifoveal traction but was less frequently identified than with surgery [128]. Clearly, observations made at the time of surgery are superior to imaging techniques when it comes to the assessment of the posterior hyaloid. It may serve as a reference to assess the positive and negative predictive values of novel imaging techniques with regard to PVD.

Influence of PVD on Macular Edema

The spontaneous release of vitreomacular traction in the presence of cystoid edema often leads to an improvement in vision [129–134]. Six studies were identified which looked at the prevalence of PVD in patients with macular edema caused by diabetic retinopathy or retinal vein occlusion [63, 135–139]. In total 615 eyes were identified. The risk of macular edema was reduced in patients with a PVD. Here, in contrast to proliferative disease, there was no significant difference between the presence of a PPVD or CPVD in terms of the associated OR (table 3).

The effect of a spontaneous PVD on the persistence of macular edema in a number of ocular pathologies (diabetic retinopathy, retinal vein occlusion, vitreomacular traction, and peripheral uveitis) was sufficiently well reported to allow analysis of 12 papers [123, 125, 126, 129, 130, 133, 140–144]. A total of 341 eyes with NPVD at the initial examination were reported with a follow-up extending for 1–110 months. Pooled analysis from these 12 studies indicates that macular edema is associated with a PPVD or absent PVD (OR 0.30, 95% CI 0.16–0.57).

PVD and Macular Holes

In stages 1 and 2 macular holes, 96% or more of eyes have only a perifoveal PVD, as shown by high-resolution OCT imaging [145]. Progression to a CPVD is a slow process potentially leading to the development of a full-thickness hole. In 31 eyes with perifoveal vitreous detachment followed prospectively, only 3 showed progression to CPVD over an average of 30 months [64]. Studies based on clinical observation alone already showed that small holes were associated with an attached posterior hyaloid. Two studies [146, 147] with a combined total of 502 eyes, compared the state of the posterior vitreous cortex (complete, partial, or absence of detachment) between patients with idiopathic macular holes and normal control subjects. A pooled analysis of these 2 studies using the fixed effects model found that patients with idiopathic macular hole were twice as likely to have an intact or partially detached posterior hyaloid (OR 0.455, 95% CI 0.314–0.660).

Three studies [65, 148, 149], on 469 eyes, looked at the state of the posterior vitreous cortex (complete detachment vs. partial or absent) in relation to the stage of idiopathic macular hole. Pooled analysis from these 3 studies found that patients with stage 1 and 2 macular holes had a significantly higher incidence of NPVD (OR 0.034, 95% CI 0.009–0.12) than stage 3 and 4 macular holes.

Four studies [140, 150–152], on 178 eyes, considered the state of the posterior vitreous cortex (PVD or NPVD) in early stages of macular hole formation (I and II) and the incidence of progression or resolution over a 3- to 240-month follow-up. Patients having a PVD or vitreofoveal separation at the initial examination or who developed a PVD during the follow-up period were less likely to progress. Absence of a PVD was associated with an OR of 0.08 and a 95% CI of 0.037–0.17. Closure of the macular hole was significantly associated with CPVD. High-resolution OCT suggests that despite a perifoveal detachment, a persistent attachment of the posterior hyaloid may remain at the edge of the hole and contribute to its progression towards stage IV. This is more frequent when an attachment persists at the edge of the optic nerve [46, 145]. Such findings are absent in macular pucker, where a CPVD is seen in a majority of patients [153].

PVD and AMD

The association between an incomplete PVD and exudative AMD was first recognized in 1996. The clinical picture was ascertained with contact lens biomicroscopy, and the state of the vitreous using a 10-MHz dynamic B scan ultrasonogram [154]. A significantly higher incidence of incomplete PVD was found in patients with macular degeneration ($p = 0.006$). We identified 4 studies that looked at the state of the posterior hyaloid in patients with macular degeneration [154–157]. Three of the 4 studies used the ultrasound to assess the posterior vitreous, while 1 study used exclusively the OCT [155]. In total 332 eyes with AMD were studied and compared to age-matched controls. The OR was 0.46 in favor of a CPVD, a similar figure to that observed with macular hole formation in affected patients versus a control population. Two studies compared exudative versus nonexudative AMD. A pooled analysis of these 200 patients gives an OR of 0.5 in favor of a PVD [157, 158]. One of these studies looked at the state of the macular area with the OCT, allowing for a more detailed analysis of anomalous vitreous insertion [157]. Partial or persistent adhesion in the foveal area was up to 10 times more likely in the exudative form of AMD. While the posterior hyaloid may play a role in wet AMD, it does not seem to have an influ-

ence on polypoidal choroidal vasculopathy, where the incidence of vitreomacular adhesion is the same between affected eyes and controls [159].

Conclusions

The vitreous and the posterior hyaloid are intimately linked to a number of ocular processes. As the largest structure within the eye, it is subjected to constant physical strain and undergoes significant changes with age. Physiological changes start early in life, and can have profound consequences on ocular homeostasis. A PVD may be of benefit in AMD, its absence is clearly associated with

an increased risk of proliferative disease in diabetes and retinal vein occlusion. For proliferative diabetic retinopathy, a PPVD is associated with a significantly higher risk of proliferation than in its absence. Medical interventions, particularly surgical ones, have already improved the prognosis in a number of these conditions. Ideally, prevention by timely induction of a PVD, prior to the onset of these ocular diseases, might significantly reduce morbidity without the need of surgery. This is what pharmacological vitreolysis may provide. Armed with the knowledge on the role of both the vitreous and the posterior hyaloid on the natural history of ocular diseases, it will be possible to assess adequately new therapeutic modalities as they become available.

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