

A large, yet little understood structure

Understanding the vitreous

Anatomy, ageing and transformation

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The vitreous is a gel-like structure that assumes four-fifths of the volume of the eye. The volume of the vitreous is approximately 4ml, with 99% of it being water; 0.9% is composed of organic salts and low molecular weight organic lipids. Approximately 0.1% of the vitreous consists of soluble and insoluble proteins, which include Type II collagen, hyaluronan and hyalocytes¹².

Anatomy

Seabag³ noted that although the vitreous is the largest structure within the eye, our knowledge of its architecture, function and role in disorders of sight is less than that for any other ocular structure. He pointed out that lack of ability to visualise the vitreous, as well as the lack of few effective techniques for its laboratory study, have limited our understanding.

The central vitreous comprises the majority of the vitreous body. It contains low concentrations of collagen fibrils, which are oriented as a loose network, in an anterior-posterior direction with insertions anteriorly into the vitreous base and posteriorly into the vitreous cortex⁴.

The vitreous cortex is a thin layer of vitreous surrounding the central vitreous. It is characterised by a higher collagen concentration than that of the central vitreous and its posterior portion is adherent to the inner retina, just posterior to the posterior border of the vitreous base, which itself straddles the pars plana. The dense collagen fibrils of the posterior vitreous cortex run parallel to the retina and are inherently attached to its internal limiting membrane.

The vitreous cortex is most firmly attached at the vitreous base. Other naturally occurring areas of more firm attachment include the margin of the optic nerve head, the macula, major retinal blood vessels and retinal tufts. Acquired areas of

increased vitreoretinal adhesion include lattice degeneration, some post-inflammatory lesions, areas of degenerative modelling, and some vitreous base lesions^{1,5}. These areas of increased adhesion may remain attached, even if the vitreous is detached elsewhere⁶.

Sebag and Balazs⁷ reported that the posterior vitreous cortex contained a round hole corresponding to the peripapillary attachment. The diameter of the hole measures approximately 1.25mm. A second hole, corresponding to a premacular attachment, was reported to measure approximately 5mm in diameter⁷. This latter hole has not been uniformly reported in subsequent literature. Clinically, the posterior vitreous cortex is best visualised after a posterior vitreous detachment (PVD) when it has separated from the retina⁸. Weiss ring describes the clinically visible hole in the detached vitreous cortex, corresponding to the former circumscribed area of peripapillary attachment (**Figure 1**).

Function

The vitreous serves as a clear optical media posterior to the lens, a stabiliser of the volume of the globe, a defence against collapse of the globe should it be perforated, a pathway for nutrients to reach the lens, and an angiogenic inhibitor^{4,8,9}.

Changes in the vitreous

Syneresis was the name ascribed to 'shrinkage' of the vitreous by early investigators¹⁰. Synchrony was an additional term, used to denote liquefaction of the vitreous gel. According to Foos¹¹, Goldmann¹² was among the first to recognise the relationship of degenerative vitreous changes to eventual PVD, a process in which the thinned posterior cortex of the vitreous finally ruptures and emits synchetic fluid into the retrohyaloid space^{13,14}.

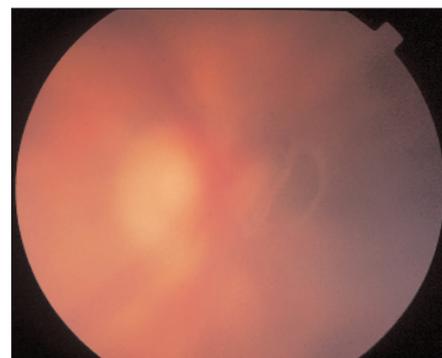
In a clinical study, Lindner¹⁵ reported the incidence of posterior vitreous detachment to be 53% in persons older than 50 years, and 65% over the age of 65 years. Autopsy

studies have confirmed the increased incidence of PVD with age, revealing an incidence of 27% in the seventh decade and 63% in the eighth decade¹¹.

Age-related PVD, not associated with inflammation, surgery, trauma or retinal disease, is predictably a consecutive phenomenon between the two eyes. Multiple studies have demonstrated subsequent PVD of the fellow eye occurring within two years of the first eye PVD in 65-88% of patients¹⁶⁻¹⁸.

Preponderance of females over males with PVD has been reported in multiple studies previously^{11,19-23}. Lindner¹⁵ has suggested that a preponderance may be the result of hormonal influence, with PVD being the result of hormonal withdrawal. However, Byer¹⁷ refutes this theory by comparing his own PVD study set of females and males to an age matched control group of new patients in the same office. Given the naturally occurring sex ratios in the general population, no statistical difference in PVD frequency could be documented between groups.

The age of onset of vitreous detachment, until recently, has been difficult to determine, particularly due to the aforementioned difficulty in evaluating its attachments clinically³. However, with new optical coherence tomography capabilities utilised to image the vitreous, Uchino *et al*²⁴ demonstrated that healthy human eyes had incomplete or partial PVD beginning in stages, as early as the fourth decade of life. Their study confirmed Foos' assertion^{11,25} that incomplete PVD begins in the macular area, presenting with an initial, focal, shallow perifoveal vitreous detachment in one quadrant.



» **Figure 1**
PVD with Weiss ring

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This early, partial PVD later expands in four stages over several years. These subsequent stages include separation from multiple perifoveal quadrants, separation from the fovea and, finally, complete separation from the disc and elsewhere. The study also found that the superior quadrant was usually the site of incomplete PVD, and that the first three stages of PVD were not visible using standard clinical examination techniques. The authors concluded that the development of PVD was not an acute event but rather a slow, asymptomatic process until completion. Yonemoto *et al*⁶ have noted a "possible tendency" toward a lower PVD onset age for females.

Age-related vs. disease-induced PVD

Two types of vitreous detachment have been previously distinguished²⁷. The first type, associated with age-related liquefaction of the vitreous, renders the configuration of the detached vitreous wavy and changeable. In this type of PVD, the retrovitreal space is wide and the vitreous gel is freely moveable with ocular motility.

The second type of PVD is associated with certain diseases such as diabetic retinopathy²⁸ and it occurs independent of age. The detached vitreous cortex remains hemispherical and parallel to the retinal surface. The retrovitreal space is narrow, and the vitreous gel is restricted in its mobility, owing to stiffness created while releasing a water-like fluid into the retrovitreal space. Although the mechanism for this type of vitreous degeneration is poorly understood, it often presents uniquely with increased flare, thought to be indicative of serum components that have leaked into the vitreous gel³. Akiba *et al*² demonstrated that calf serum injected into bovine vitreous caused vitreous gel contraction and release of water like fluid. The authors hypothesised that the serum promoted cross-linking of collagen within the vitreous, leading to a contraction and hardening of the vitreous gel.

Using biomicroscopy²⁹ and vitreous photography techniques³⁰ on 400 human patients, Kakehashi *et al*³¹ identified a classification of PVD into four separate types, some of which were significantly associated with vitreoretinal disease:

1. COMPLETE PVD WITH COLLAPSE:

This type demonstrates vitreous gel liquefaction, a large retrovitreal space and smooth movement of detached vitreous associated with eye movement. A Weiss ring is typically present and the posterior vitreous cortex assumes a wavy, sigmoidal shape. This type is commonly seen in eyes with age-related changes and high myopia.

2. COMPLETE PVD WITHOUT COLLAPSE:

This type demonstrates minimal gel liquefaction and limited movement of the

detached vitreous. The retrovitreal space is narrow and clinically defined only when the vitreous shrinking is advanced. Weiss ring is typically present and the posterior vitreous cortex is convex. This type is most commonly seen in eyes with uveitis and central retinal vein occlusion.

3. PARTIAL PVD WITH A THICKENED POSTERIOR VITREOUS CORTEX:

This type demonstrates a thickened, taut posterior vitreous cortex which is anchored at two variable points of attachment, including the vitreous base, the optic disc, along the vascular arcade, a neovascular complex, and the macula. This type is most commonly seen in eyes with proliferative diabetic retinopathy.

4. PARTIAL PVD WITHOUT THICKENING POSTERIOR VITREOUS CORTEX:

This type demonstrates two points of attachment as in Type 1, this type is most commonly seen in eyes with age-related changes without retinal disease.

Kakehashi³² reiterated, in a later paper, that the Weiss ring was not always visible in patients with PVD and that slit lamp visualisation of the optically empty retrocortical space was essential in making the diagnosis of PVD.

Clinical changes in the vitreous

The pathogenesis of PVD is associated with changes within the vitreous that are visualised as liquefaction, or Synchysis, as well as the breaking of the adhesion between the vitreous cortex and internal limiting membrane. As the collagen fibril network of the vitreous gel destabilises, liquid pockets called lacunae begin to replace the once gelatinous vitreous body. With increased Synchysis, eventual collapse of the vitreous body can occur⁴.

Like eventual PVD, vitreous liquefaction is associated with increased age. Liquefaction of the vitreous may begin as early as four years of age with liquefied vitreous increasing to 20% of total volume by age 20³³. An autopsy study by O'Malley²² revealed more than half of the vitreous was liquefied in 25% of individuals between the ages of 40 and 49, and in 62% of individuals aged between 80 and 89.

Sebag³⁴ examined and photographed the clinically evident morphologic changes in the vitreous of 59 autopsied eyes. He found the vitreous to be homogeneous and transparent in many individuals younger than 30 years. The vitreous of middle-aged individuals had macroscopic, visible fibres centrally, demonstrating anatomic insertions anteriorly into the vitreous base and posteriorly into the posterior vitreous cortex. Senescent vitreous displayed reduced volume, syneresis, thickness and tortuous fibres, and increased quantities of liquefied vitreous. Condensed bundles of

collagen fibrils, moving in the liquefying vitreous, are often perceived by patients as floaters (**Figure 2**). Sebag theorised that these visible age-related changes of the vitreous were most likely from a progressive reorganisation of hyaluronic acid and collagen molecular networks.

Molecular changes

An ordered meshwork of loosely tied collagen fibrils is presumed to maintain vitreous gel transparency and volume. Scott³⁵ compares the loose, but organised pattern of collagen fibrils in the human vitreous, tied together by proteoglycan bridges, to the organisation of the corneal collagen fibrils. The cornea contains thicker and more numerous collagen fibrils, exactly parallel and at constant, interfibrillar separations contained in lamellae, which are ordered at right angles to each other. When the arrangement of either scenario is disrupted, the transparency of either tissue is compromised. Within the vitreous, change in the interfibrillar organisation and spacing may also result in liquefaction.

Liquefaction of the vitreous, visualised by multiple, individual pockets of liquid, begins in the vitreous body. The lacunae eventually coalesce, while the normally separated collagen fibrils begin to fulfill their natural tendency to aggregate. The vitreous body begins to shrink. Simultaneously, a weakness of the vitreoretinal adhesion develops between the cortical vitreous and the internal limiting membrane. Both processes culminate into a PVD.

Hyaluronic acid is vulnerable to free-radical damage. Such damage, Scott³⁵ notes, may arise from a small amount of radiation, perhaps from incident light as well. Damage to the hyaluronic acid may interfere with its contribution to the collagen meshwork configuration in the



» Figure 2
Vitreous floater

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vitreous and incite subsequent breakdown, liquefaction and detachment.

Although the mechanism for PVD still remains unknown, Bishop³⁶ has argued that the process of liquefaction and vitreoretinal adhesion weakening may both be related to changes in structural macromolecules on the surface of vitreous collagen fibrils, as well as changing properties of the collagen fibrils themselves.

Bishop reiterates that collagen fibrils have a natural 'stickiness', or tendency to aggregate. Therefore, he reasoned that there must be some component preventing such aggregation in the vitreous. He pointed to opticin³⁷, an extracellular matrix leucine-rich repeat protein which is diffusely coated on the surface of vitreous collagen fibrils. Bishop asserted that opticin was instrumental in preventing collagen fibril aggregation, and therefore it maintained the gel structure and the vitreoretinal adhesion. He refuted hyaluronan's alleged role in this regard, citing his own work with *Streptomyces hyaluronan lyase*³⁸. This enzyme digested the hyaluronan meshwork of the vitreous, but left behind an intact gel structure. Bishop concluded that, although hyaluronan was not necessary for the maintenance of long range fibrillar spacing, it most likely increased the molecular stability of the gel.

If the opticin coating was damaged, either by ageing or another mechanism, the collagen fibrils would not then be repelled from one another and aggregation of fibrils would ensue, giving way to vitreous liquefaction, Bishop stated³⁶. Furthermore, altered opticin within the collagen of the vitreoretinal adhesion might also yield a weakening of the adhesion and subsequent PVD.

Future studies on collagen-associated macromolecules may shed light on the mystery of the exact mechanism which incites PVD.

Retinal complications from PVD

Partial and complete vitreous detachment pose risks for the development of vitreomacular traction syndrome, retinal tags, avulsion of retinal vessels, vitreous haemorrhage, pre-retinal haemorrhage, cystoid macular oedema, macular cysts and macular holes^{18,39-42}. Urgent complications associated with PVD include retinal tears and subsequent retinal detachments (Figure 3)^{17,43-48}.

The prevalence of retinal breaks associated with PVD is reported to be 10-34%⁴⁹. Reported percentages vary with study type, sample size and inclusion criteria. Moreover, untreated, symptomatic retinal breaks progress to retinal detachments in 33-46% of cases⁵⁰.

The incidence of complications of acute PVD depends on the extent and strength of pre-existing vascular and paravascular

vitreoretinal attachments. If the adhesions are strong, the retina may be torn or blood vessels avulsed. Early reports by Morse and Scheie⁴⁷ recommended prophylactic treatment of all retinal breaks, even if asymptomatic, if a PVD had yet to occur in the affected eye. However, Byer⁴⁵ later found no tendency for PVD to provoke complications with pre-existing tractional or non-tractional retinal breaks, such as operculated holes or holes within lattice. Therefore, Byer concluded that prophylactic treatment of all retinal breaks could not be justified just because a PVD was not yet present.

Subsequent or delayed retinal tears may develop after the initial, symptomatic PVD-related tears^{44,46}. Goldberg and Boyer⁴⁶ noted a 9.6% development of sequential retinal breaks, the majority of which occurred within three months of the initial breaks, indicating sustained vitreoretinal traction. Sharma *et al*⁴⁴ found a 12% incidence of subsequent retinal tears, the majority of which occurred six months after initial treatment for PVD-related retinal breaks. The authors presented three plausible explanations for their findings: (1) PVD may be incomplete on the first visit, yielding the potential to cause further pathology as it continues to detach; (2) therapeutic intervention may play a role in subsequent retinal tear development; and (3) the 'newly discovered' pathology may have already been present, but undiagnosed during the initial visit. The authors pointed out that some subsequent retinal tears were asymptomatic, and thus incidental findings on repeat examination, highlighting the importance of timely follow-up.

Prognostic symptoms and signs

Byer¹⁷ found that in a series of 163 patients who had only one to two floaters as a presenting symptom, with or without

flashes, a retinal tear was diagnosed in 7.3% of cases. Twenty-one percent of patients who went on to develop retinal detachments reported only one to three floaters and light flashes as their only symptoms for 2.5 to three weeks preceding visual field loss.

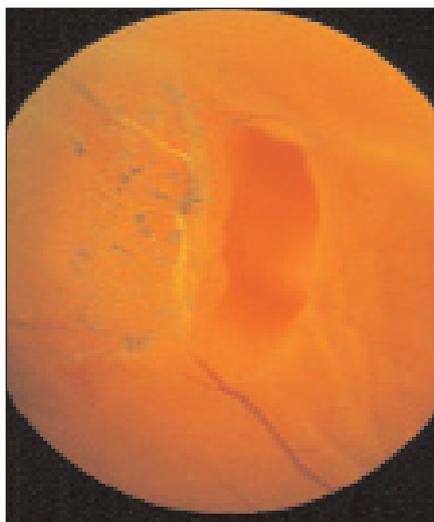
Dayan *et al*⁵¹ reported that subjective reduction in vision, regardless of Snellen equivalent, was more predictive of posterior segment pathology in their series of 189 PVD patients. Compared to patients with retinal breaks reporting flashes and floaters alone (23%), 67% of patients with flashes and/or floaters with a subjective reduction in vision had retinal breaks at initial presentation of PVD. The authors suggested that the perceived reduction of vision without retinal detachment may be related to small amounts of vitreous haemorrhage, pigment or the breakdown of the blood-vitreous barrier with resultant vitreous flare.

Hikichi *et al*⁵⁰ demonstrated a prevalence of vitreous haemorrhage associated with PVD-related retinal breaks. Vitreous haemorrhage accompanied retinal breaks in 71% of patients with symptoms of floaters alone, and 70% of patients with both symptoms of flashes and floaters.

Tanner *et al*⁵² reviewed 200 phakic eyes with recent onset PVD. They conclude that it was not possible to predict which patients would have a retinal break based on symptoms alone. They utilised dynamic vitreous gel examination at the slit lamp to determine the presence of Shafer's sign⁵³, that is, pigment from the RPE, located at the anterior vitreous. Because the amount of pigment can be small, it may have a propensity to settle at the bottom of the globe. Existing pigment in the vitreous can more readily be brought into view at the slit lamp by having the patient move fixation, and therefore the vitreous itself. Distinguishing pigment cells from red blood cells may be accomplished by recognition of the larger, darker and more irregular shape of the pigment cells. The authors noted that the use of Shafer's sign yielded a 95.8% sensitivity, and a 100% specificity, for the presence of retinal breaks associated with PVD of recent onset.

Accelerators of PVD

Morita *et al*⁵⁴ investigated the correlation of age, axial length and myopic chorioretinal atrophy associated with vitreous changes. The study encompassed 329 eyes of highly myopic persons (greater than -8.25D) and axial length exceeding 26mm. They confirmed that liquefaction of the vitreous began at a relatively young age in patients with high myopia. Specifically, they noted a 12.5% prevalence in highly myopic patients aged 20 to 29. This was progressive with age and axial elongation, thus resulting in a frequent occurrence of PVD. Myopic chorioretinal atrophy was not significantly related to the development of vitreous



➤ **Figure 3**
Retinal tear caused by PVD

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liquefaction or PVD.

Akiba⁵⁵ studied 224 eyes with myopia over -6.00D. He found that PVD may develop nearly 10 years earlier in highly myopic eyes, as compared to emmetropic eyes. The reason for earlier PVD development in high myopia remains uncertain. Possible mechanisms may be related to an increase in vitreous volume, varied hyaluronic acid quantities in myopes and unique variations in vitreoretinal adhesions in high myopes⁵⁶.

The progression of vitreous syneresis may also be accelerated by intraocular inflammation due to surgery, other trauma, uveitis and connective tissue disorders⁵⁷.

Internal post-saccadic vitreous movement is dampened by the bulging convexity of the human crystalline lens. This structural relationship reduces the torsional forces acting on the various vitreous attachments during subsequent vitreous deceleration following a saccade¹. Hence, removal of the lens likely leaves aphakic patients, and possibly pseudophakic patients more vulnerable to vitreous traction and PVD⁵⁸.

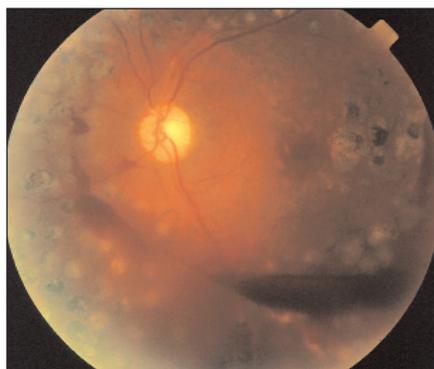
It has been postulated that YAG laser, which increases the risk of iatrogenic retinal detachment, may do so via laser induction of a PVD⁵⁹. This was contradicted by Sheard *et al*⁶⁰, whose prospective study demonstrated that Nd:Yag capsulotomy was not associated with an increased incidence of new PVD.

Acoustic shock waves generated during refractive excimer laser keratectomy have been investigated as possible instigating mechanisms which might lead to retinal detachments or worsening of existing pathology⁶⁰. The pathologic basis for this remains uncertain, and reports since then have not found a causal link between corneal surface ablative procedures and vitreoretinal pathology including iatrogenic PVD⁶¹⁻⁶³.

Sebag *et al*⁶⁴ reported that in a 30 eye

diabetic case series, panretinal photocoagulation (PRP) was directly associated with vitreous detachment, irrespective of the severity of diabetic retinopathy or prior vitreous haemorrhage. Moreover, the incidence and extent of the PVD increased with increased amounts of PRP. The authors hypothesised that liquefaction and weakening of the vitreoretinal interface may be precipitated by the PRP application (Figure 4).

Pharmacologic induction of PVD may be caused by dispase, a neutral 35.9kD protease. The enzyme is obtained from *Bacillus polymyxa*, which cleaves basal membranes containing Type IV collagen and fibronectin. Intravitreal injection of dispase was shown to cleave the attachment of the posterior hyaloid and the internal limiting membrane in 20 human cadaver eyes within a 15-minute interval. The vitreous gel, consisting of Type II collagen, was not liquefied and the viability of the adjacent retina was left intact. The utility of this enzyme in the management of patients with vitreoretinal disorders, such as diabetic



» Figure 4
PVD with vitreous haemorrhage following laser treatment

retinopathy and vitreomacular traction, remains to be investigated⁶⁵.

Scheduling repeat examination

If a patient has an acute symptomatic PVD of less than one month, and no vitreous haemorrhage or retinal break is detected on initial dilated indirect ophthalmoscopy, a repeat examination in one month may be considered⁶¹. Regarding patients with vitreous haemorrhage in the setting of acute PVD where no retinal tears are detected, follow-up examination in two to three weeks, and then at regular intervals until the entire retina is visualised, may be considered⁶². If vitreous pigment is visualised, accompanying a PVD, the examiner should assume a retinal break is present and the patient should be referred immediately for expert retinal examination⁶².

In the interim between follow-up examinations, patients who have experienced PVD should be well educated on the symptoms warning of possible retinal complications. These include flashes, floaters, decreased vision and visual field defects. Should these symptoms arise, patients should be instructed to contact their practitioner for immediate repeat dilated fundus examination^{17,51}.

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Visit www.optometry.co.uk/references.