Proliferative Diabetic Vitreoretinopathy

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Outline

Keywords
Vitreous • Retina • Diabetes • Diabetic vitreopathy • Proliferative diabetic vitreoretinopathy • Clinical staging • Neovascularization • Vascular endothelial growth factor

Key Concepts

1. Vitreous play a critical role in proliferative diabetic retinopathy, and thus, the appropriate term for this condition is proliferative diabetic vitreoretinopathy (PDVR).
2. A clinical classification of PDVR is proposed, which predicts surgical outcomes in advanced cases.
3. Treating diabetic vitreopathy may be a useful adjunct to treatments of diabetic retinopathy so as to mitigate the contribution of vitreous and improve long-term prognosis.

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I. Introduction

This chapter reviews the pathogenesis of proliferative diabetic vitreoretinopathy (PDVR) and presents recommendations for its clinical staging. Although numerous biochemical mediators may be responsible for the pathogenesis of PDVR, there is no consensus about the biochemical pathway(s) responsible for the progression of PDVR. Among the known and most studied mediators is vascular endothelial growth factor (VEGF) [18]. Since the thickened posterior vitreous cortex is one of the main components in proliferative diabetic retinopathy (PDR) causing the subsequent development of retinal proliferations, shrinkage of the diabetic posterior vitreous cortex leads to traction retinal detachment. Although several classifications are described in the literature, the

J. Sebag (ed.), *Vitreous: in Health and Disease*,
DOI 10.1007/978-1-4939-1086-1_24, © Springer Science+Business Media New York 2014

classification suggested herein is important in the clinical assessment of disease severity, communication about the disease state, and the evaluation of therapy. A new morphological classification of PDVR is presented which emphasizes the role of vitreous, hence the name PDVR. Moreover, this classification reliably predicts the surgical outcome in advanced stages of PDVR.

A. Diabetes

Diabetes is a metabolic disease that affects juvenile (type I) or adult patients (type II) throughout their lives, and is increasing worldwide [21, 22, 23, 36]. Several clinical trials in Europe and North America like EURODIAB Prospective Complication Study 1998; WESDR (*Wisconsin Epidemical Study of Diabetic Retinopathy*) [27]; DCCT (*Diabetes Control and Complication Trial*) *1996*, *UKPDS United Kingdom Prospective Diabetes Study*) [62, 63]; ETDRS (*Early Treatment Diabetic Retinopathy Study*); and a Japanese group [39] demonstrated that the most important risk factor for the beginning and progression of diabetic retinopathy (DR) is the level and duration of hyperglycemia over years. Additional factors for the progression of DR are elevated blood pressure, especially an increased systolic blood pressure. Elevated lipids, microalbuminuria, and high ocular perfusion pressure also influence the progression of diabetic angiopathy [60]. Further, growth hormones stimulate the production of insulin-like growth factor, which may play a role in the pathogenesis of DR [5, 69].

At disease onset, diabetes remains predominantly a metabolic disease. However, after approximately five years, or in childhood after puberty, severe secondary changes in the vessels of the brain, heart, kidneys, inferior extremities, and especially in the eyes may occur, leading to dramatic complications either isolated or multiple in the affected organs [30, 31]. If the eyes of a diabetic patient become affected, the vascular changes start in the retina with signs of DR, less seldom are changes in the iris such as rubeosis iridis or iris neovascularization. However, vitreous changes occur even earlier in the natural history of disease [see chapter I.E. Diabetic vitreopathy].

B. Diabetic Retinopathy

The broad spectrum of clinical signs in diabetic retinopathy (DR) ranges from biomicroscopic changes of intraretinal capillaries to severe proliferation of new vessels out of the retina into the vitreous, leading to vitreous hemorrhage and traction retinal detachments, which may cause severe loss of sight (Figure III.L-1). DR has traditionally been subdivided into nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). While NPDR is characterized by a retinal microangiopathy with intraluminal, intramural, and extramural pathologies, PDR is predominantly characterized by proliferation of vessels onto the retinal surface and into the posterior vitreous cortex. Concurrent with these retinal changes is a separate set of pathologic changes in vitreous, known as diabetic vitreopathy [46] [see chapter I.E. Diabetic vitreopathy]. Since, PDR develops only if the vitreoretinal interface is partially or completely attached to the retinal surface to provide a scaffold for new vessel proliferation, we recommend including the impact of vitreous in clinical nomenclature and call this stage "proliferative diabetic vitreoretinopathy" (PDVR).

1. Nonproliferative Diabetic Retinopathy (NPDR)

NPDR usually appears 5 years after the beginning of the metabolic disorders, in juvenile diabetes mellitus typically shortly after puberty. Pathogenic mechanisms include increased aggregation of erythrocytes and platelets, elevated fibrinogen activity, and thickening of the retinal capillary basement membranes, presumably due to an accumulation of glycosylated proteins. Loss of pericytes outside and a loss of endothelial cells inside the retinal capillaries are the first changes in the retina weakening of the vessels wall, resulting in microaneurysms, venous abnormalities, intraretinal hemorrhages, and leakages of serum, leading to hard exudates and an accumulation of lipoproteins in retinal layers. Finally, there are so-called intraretinal microvascular abnormalities (IRMAs), characterized as arteriovenous shunts in areas of occluded retinal capillaries and early intraretinal neovascularization.

Clinical classification of these retinal abnormalities [7] is important for prognosis (45 % of patients with severe NPDR as defined by the University of Wisconsin 4:2:1 rule [9] progress to PDVR within one year) and to define indications for laser therapy [9]. It is currently not known whether diabetic vitreopathy plays a role in NPDR, but future research should be directed to address this question. It is suspected, however, that vitreoschisis [50] plays a role in diabetic macular edema [52], the most common cause of vision loss in diabetes [see chapter III.K. Vitreous in retino-vascular diseases and diabetic macular edema].

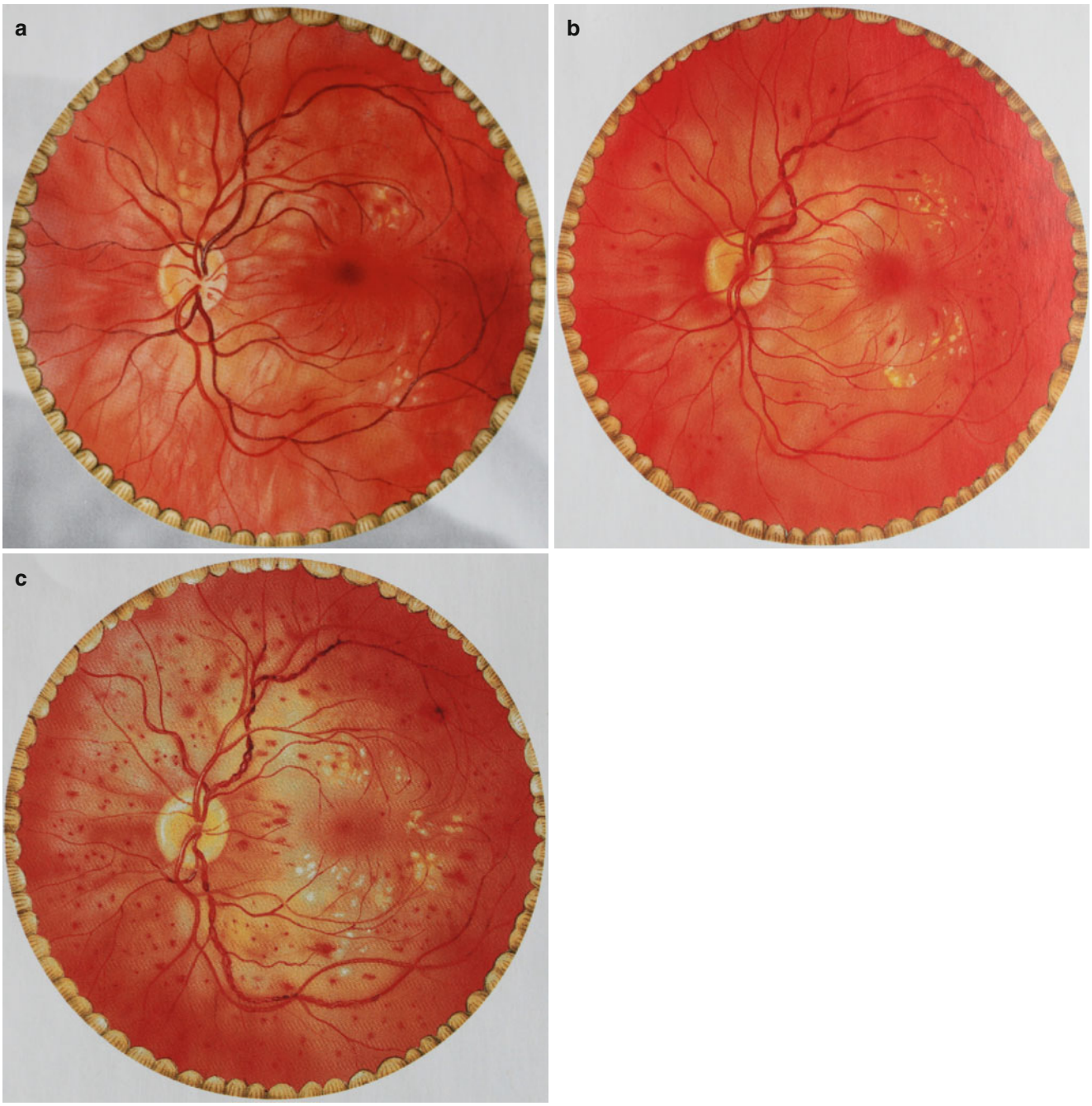

Figure III.L-1 (**a**) DR (diabetic retinopathy) mild; (**b**) DR moderate, (**c**) DR severe

2. Proliferative Diabetic Vitreoretinopathy (PDVR)

There is general agreement that the progression from NPDR to PDVR occurs approximately 15–20 years after the onset of uncontrolled diabetes, in 5–10 % of patients with type II diabetes and in 30 % of patients with type I diabetes [27]. Furthermore, diabetic patients with PDVR in one eye are at high risk of developing neovascularization in the second eye over a 5-year period, so close follow-up and early treatment are highly recommended [17, 65].

II. Role of Vitreous in PDVR

The progression from NPDR to PDVR is marked by two different processes:

I. In early stages, there is thickening of the posterior vitreous cortex, a change seen only in diabetic eyes (Figure III.L-2) [19]. Since the healthy vitreous contains antiangiogenic properties, vessels are absent in health [40, 69]. Thickening of the posterior vitreous cortex is believed to alter these properties and promote the ingrowth of proliferating vessels out from the retinal surface into the thickened posterior vitreous cortex itself [11, 14, 29, 37].

II. In a second set of events, the altered and thickened posterior vitreous cortex begins to shrink, possibly induced by factor 13 of the hematopoietic system [2], leading to traction and rupture of proliferating vessels inducing intravitreal hemorrhage or even traction retinal detachment.

The healthy posterior vitreous cortex consists of a dense matrix of collagen fibrils which are attached to the retina via an extracellular matrix [42, 53] [see chapter II.E. Vitreo-retinal interface and inner limiting membrane]. This tight attachment is mediated by extracellular matrix proteins, mainly fibronectin and laminin [20] (Figure III.L-2). Long-standing diabetes alters proteins throughout the entire body including in vitreous. Sebag et al. were the first to show the increased levels of advanced glycation end products in human diabetic vitreous as compared to controls [43, 45]. These biochemical abnormalities induce structural changes within the vitreous body [44] and likely at the vitreoretinal interface, perhaps similar to what has been identified during aging [42]. There is also a breakdown of the blood-retinal barrier. Serum proteins like fibronectin accumulate up to ten-fold between the posterior cortex and the inner limiting membrane (ILM) of the retinal surface, especially in the temporal and nasal quadrants [20, 70]. At the same time, increased levels of laminin and type I and type IV collagen become apparent [4]. These accelerate the thickening of the vitreoretinal interface, leading to an additional metabolic barrier between retina and vitreous [see chapter IV.A. Vitreous physiology].

Several clinical and experimental investigations have clearly demonstrated that the thickened posterior vitreous cortex together with the thickened extracellular matrix at the vitreoretinal interface (see chapter II.E. Vitreo-retinal interface and inner limiting membrane] plays a key role in angiogenic pathogenesis [10]. The first step involves angiogenic growth factors activating the endothelial cells to release specific protease enzymes, which promote the breakdown of basement membranes [66], allowing the endothelial cells to leave the vascular wall, migrate into the adjacent extracellular matrix where they proliferate, and build neovascular formations (Figure III.L-3). Initially, the endothelial cells of the

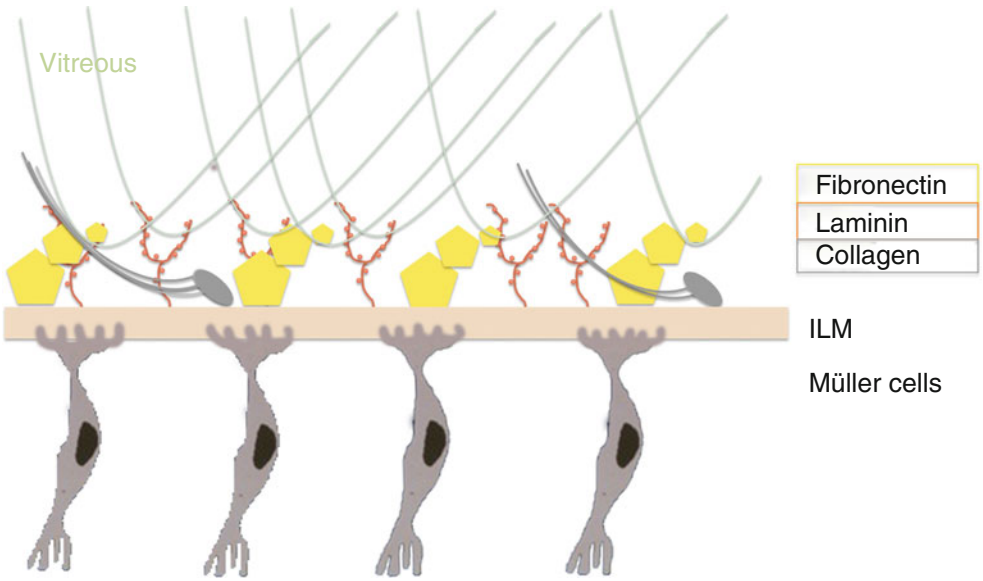

Figure III.L-2 Vitreoretinal interface: the vitreoretinal interface is believed to play a key role in the development of PDVR

retinal capillaries penetrate predominantly affected ischemic retinal areas mainly by the action of proteolytic enzymes upon the basal membrane of diabetic vessels. This early proteolytic process is followed by a proliferation through the ILM onto the retinal surface and further through the vitreoretinal interface into the posterior vitreous cortex, taking advantage of adhesive molecules, such as adjacent integrins. There are also many additional cofactors, which are responsible for this process such as growth factors, e.g., vascular endothelial growth factor (VEGF) [32, 33], transforming growth factor (TGF ß), platelet-derived growth factor (PDGF), endothelial growth factor (EGF), interleukin 1 (IL-1), angiotensin II, or somatostatin) [see chapter IV.C. Vitreous and iris neovascularization]. In this context, it has been demonstrated that Müller cells release a large amount of VEGF in ischemic areas [68] and in the presence of advanced glycation end products [12, 13, 43]. At this stage, the posterior vitreous cortex appears on biomicroscopy as a thickened preretinal membrane, especially around the optic disk and along the temporal retinal vessel arcades [70]. This scaffold facilitates additional formations of proliferating vessels in this ongoing PDVR process [10].

The second step in PDVR development starts with shrinkage of the altered posterior vitreous cortex, possibly via cross-linking of collagen fibrils. Akiba et al. [2] postulated that factor 13 (transglutaminase) of the hematopoietic system might trigger this collagen cross-linking. These advanced changes of the vitreoretinal interface by means of thickening and shrinkage lead to a potentially fateful course for the diabetic eye: the shrinking vitreous induces traction on proliferating retinal vessels inducing severe hemorrhages into the vitreous body. Additionally, vitreous shrinkage in combination with firm vitreoretinal adhesions may induce vigorous forces leading to severe traction retinal detachments, vitreopapillary traction [25, 34], and foreshortening of retina leading to a proliferative vitreoretinopathy (PVR)-like configuration. The combination of firm vitreous traction and PVR may cause retinal tears and severe combined traction/rhegmatogenous retinal detachments.

To prevent progression from NPDR to PDVR, one can perform panretinal laser photocoagulation (PRP). One therapeutic effect of this treatment is the destruction of retinal cells in areas of retinal hypoxia, especially Müller cells which are responsible for upregulation of VEGF [57–59]. Another therapeutic effect of PRP laser therapy is the induction of posterior vitreous detachment (PVD). Clinical studies [41] have shown a higher incidence of PVD following PRP. Progression of PVD can be observed 3–6 months following PRP [28]. These benefits of PRP give further support to the concept that vitreous plays a

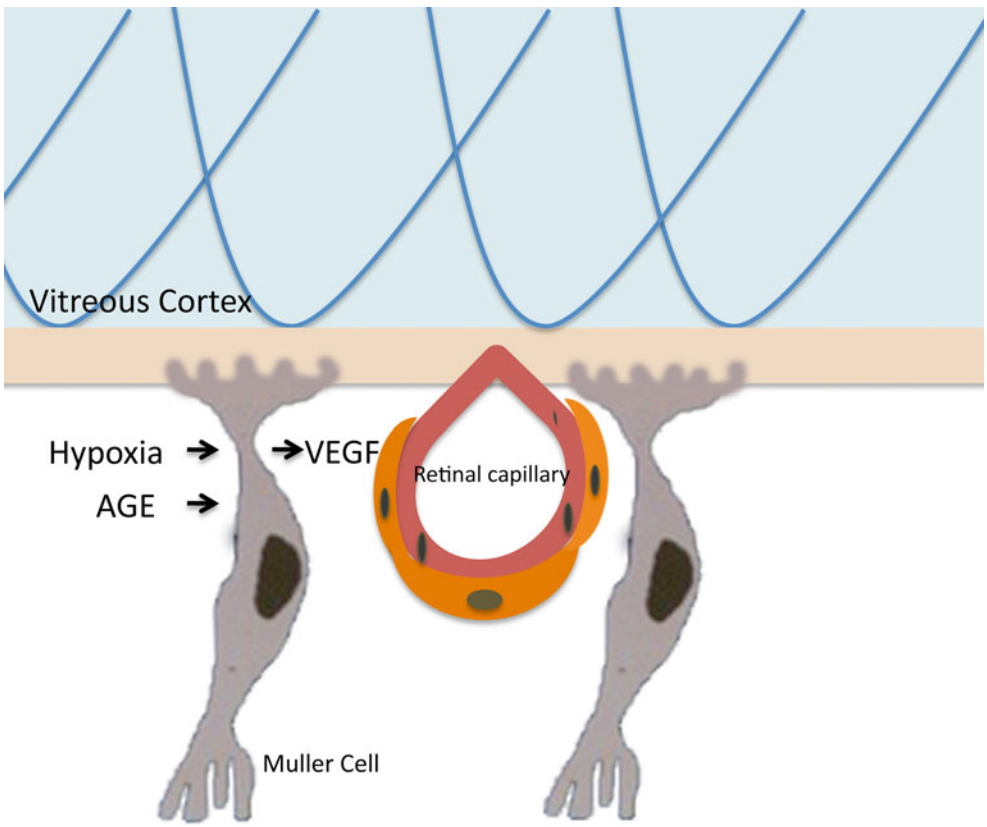

Figure III.L-3 Vascular endothelium crossing two basement membranes

role in the progression of severe NPDR to PDVR. It is of further interest to consider cases of NPDR that do not progress:

- Eyes with high myopia (>−10 diopters) rarely develop PDVR [70], since PVD frequently occurs long before diabetic retinopathy develops in elderly eyes with type II diabetes.
- Eyes with previous rhegmatogenous retinal detachment, usually due to PVD, do not develop PDVR. Conversely, diabetic patients with NPDR rarely develop rhegmatogenous retinal detachments, as their posterior vitreous frequently remains attached.
- Vitrectomized diabetic eyes rarely develop PDVR.

A. Classification of PDVR

1. Airlie House Classification

In the late 1960s, the first classification for diabetic retinopathy, the Airlie House Classification, was established [35]. Since vitrectomy was not yet introduced at that time, only the results of photocoagulation or laser coagulation therapy could be assessed by this classification. This as well as the classification of Sevin et al. [54] and the modified Airlie House Classification of the *Diabetic Retinopathy Study Research Group* [7] were only applied to diabetic eyes with vascular changes in or just outside the retina. All these classification systems were used for major multicenter studies in the 1970s and 1980s to evaluate the benefits mainly of laser coagulation treatments, *primarily the Diabetic Retinopathy Study* (*DRS*) and *the Early Treatment Diabetic Retinopathy Study* (*ETDRS*). Vitreous abnormalities, however, were not considered in these classifications systems. When vitrectomy became available, vitreous was indirectly taken into consideration when studies such as the Diabetic Retinopathy Vitrectomy Study (DRVS) and ETDRS evaluated the positive effect of this new surgical option [3]. However, both study groups, especially the ETDRS group, classified the proliferative form of DR only into early, high-risk, and severe proliferative diabetic retinopathy, based on the criteria of the Airlie House Classification. Different forms of retinal detachments, either traction or rhegmatogenous components, were considered during this classification. The ETDRS grouped all severe cases with retinal detachments, traction, iris neovascularization or fundus obscurations under "advanced PDR" without further subclassification. In 1983, Shea proposed the approach of an "early vitrectomy" in patients with diabetic retinopathy in order to improve surgical outcome and preservation of useful sight, without indicating the exact threshold for therapeutic intervention [8].

2. International Clinical Diabetic Retinopathy Severity Scale

At the turn of the century, Wilkinson et al. established another classification called the "International Clinical Diabetic Retinopathy Severity (ICDRS) Scale" during a workshop in 2003 [67]. A result of the American Academy of Ophthalmology Diabetes 2000 initiative, this classification system defined mild, moderate, and severe nonproliferative diabetic retinopathy (see Table III.L-1). There was also a stage for "no retinopathy" and a classification for "proliferative diabetic retinopathy." Numerous studies used the ICDRS scale to report comparable results among different centers. Zehetner et al. [71] evaluated the reliability of this classification and correlated the stage of the diabetic retinopathy with the concentrations of glycosylated hemoglobin (HbA1c) and VEGF level in blood plasma samples. They determined that poor glycemic control was positively correlated with increased VEGF plasma levels in patients with type II diabetes. The highest individual VEGF measurements were found in patients with severe forms of proliferative DR. Quellec et al. [38] used a modified automated ICDRS scale algorithms and confirmed a high intraobserver agreement ($\kappa = 0.769$) among young and experienced clinicians, making this classification reliable and applicable. However, this severity scale still did not propose subdividing proliferative disease into further subgroups for the proliferative diabetic retinopathy as diabetic vitreopathy was still not considered.

3. Kroll's Classification

In 1987 Kroll first proposed a classification system with subdivision of proliferative diabetic retinopathy according to the proliferative vitreoretinopathy (PVR) classification. This was further specified in greater detail in 2007 (Figure III.L-4a–c). This classification is easy to understand, can be easily explained to patients and their relatives, and helps to communicate disease progression among retinal specialists. It also helps to define thresholds for therapeutic intervention, i.e., whether laser therapy is still indicated or if vitrectomy, especially an early vitrectomy, should be performed. It furthermore serves as a predictor of surgical outcomes and can be useful for evidence-based approaches to clinical research and care [15].

Since the thickened posterior vitreous plays an important role in the pathogenesis of the proliferating form of diabetic retinopathy, the term *proliferative diabetic retinopathy* has been modified into the more precise term proliferative diabetic vitreoretinopathy (PDVR) [24, 26, 47]. Four stages are defined:

Stage A (Figure III.L-5a, b) denotes a completely attached retina, with a thickened posterior vitreous cortex. Remarkable in this stage are the proliferating vessels emanating from the retina into the posterior vitreous

Table III.L-1 Comparison of different classifications of nonproliferative and proliferative diabetic retinopathy and important studies with various stages for their inclusion criteria

International Clinical Diabetic Retinopathy Disease Scale according to AAO						
No retinopathy	Mild NPDR	Moderate NPDR	Severe NPDR	PDR		
Clinical disease severity scale of diabetic retinopathy according to ETDRS criteria						
No retinopathy	Mild NPDR	Moderate NPDR	Severe NPDR	Early PDR	High risk PDR	Severe PDR
Severity of PDVR according to Kroll						
No retinopathy	Mild NPDR	Moderate NPDR	Severe NPDR	PDVR A	PDVR Bt PDVR Bn	PDVR C1 - 4
DDCT type 1 DM UKPDS type 2 DM			DRS			
	ETDRS				DRVS	

PDVR proliferative diabetic vitreoretinopathy, *DM* diabetes mellitus

The upper part of the table shows three classification systems of diabetic retinopathy. The lower part lists important studies dealing with various stages of diabetic retinopathy. All studies have an evidence of 1b. The Diabetes Control and Comparison Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) investigated with mild and moderate cases of nonproliferative diabetic retinopathy (NPDR), the diabetic retinopathy study (DRS) with severe NPD to high-risk proliferative diabetic retinopathy (PDR). The Early Treatment Diabetic Retinopathy Study (ETDRS) on the other side investigated cases of mild, moderate, and severe NPDR and cases of early PDR. Finally the Diabetic Retinopathy Vitrectomy Study (DRVS) was performed on patients with high-risk and severe PDR

cortex, especially near the optic disk reaching to the nasal side of the posterior pole of the eye [26], but also in the area of the superior and inferior temporal arcade retinal vessels.

Stage B (Figure III.L-6a–c) is characterized by shrinking of the vitreous cortex and traction retinal detachments either in the nasal (n) (*stage B n*) or temporal side (t), in the area of the temporal arcade vessels, (*stage B t*) or at the optic

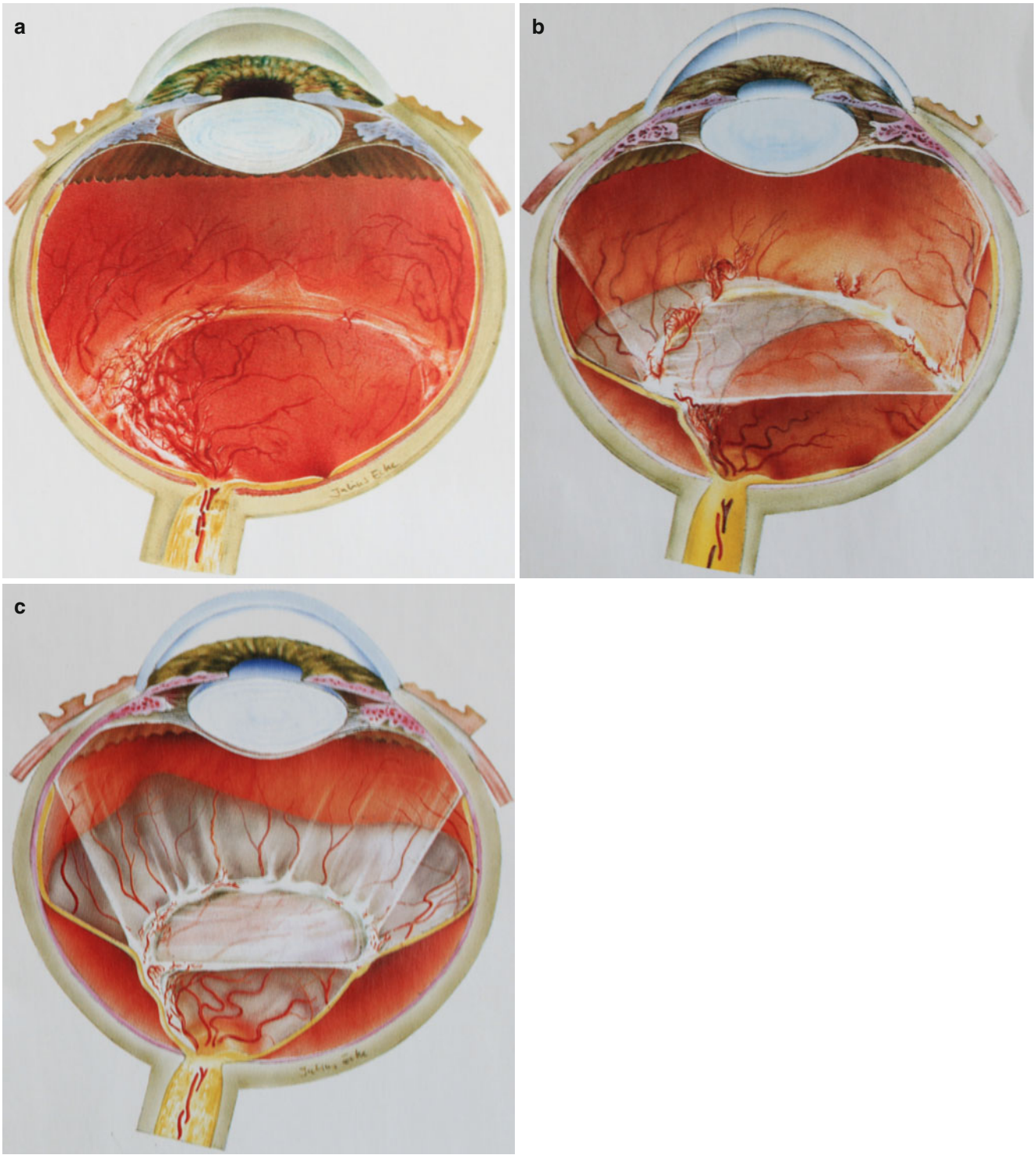

Figure III.L-4 (**a**–**c**) Stages A, B, C

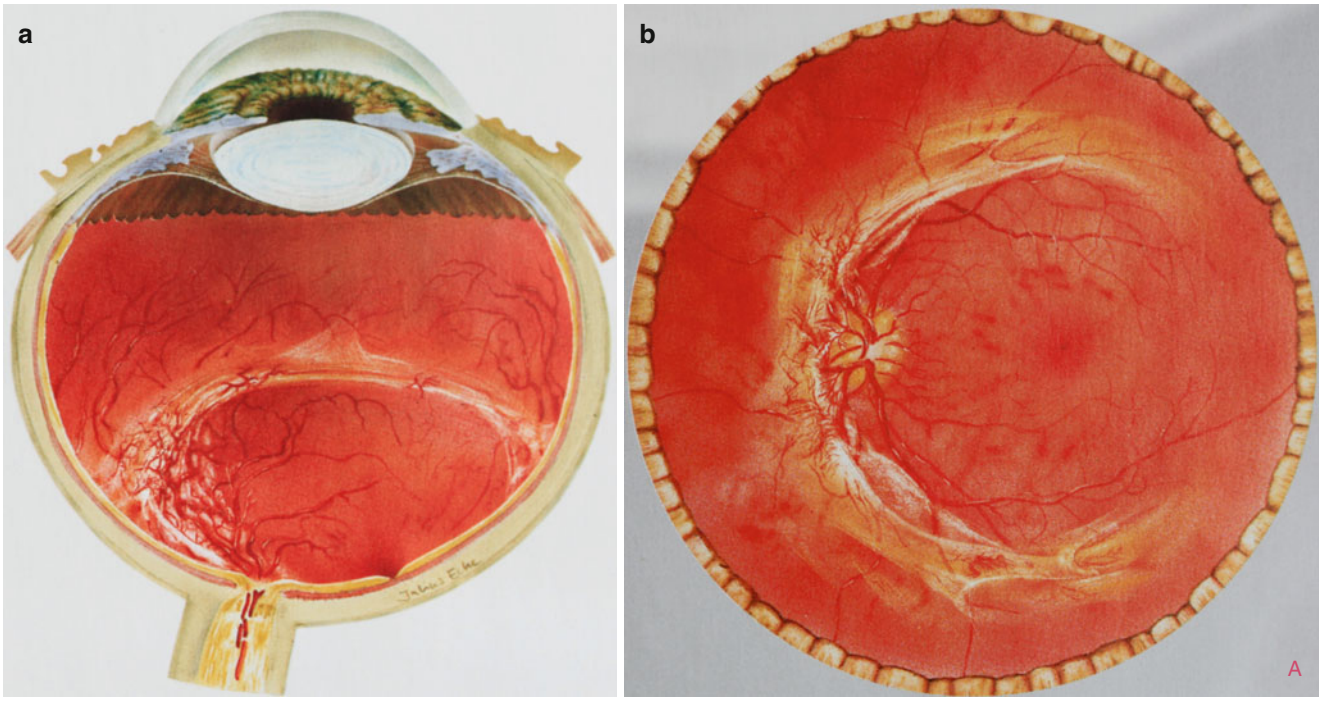

Figure III.L-5 (**a**, **b**) Stage A Figure III.L-2. PDVR, stage A: this stage is characterized by proliferative changes in vitreous and retina, especially around the optic disk and in the posterior vitreous cortex. The retina is still totally attached

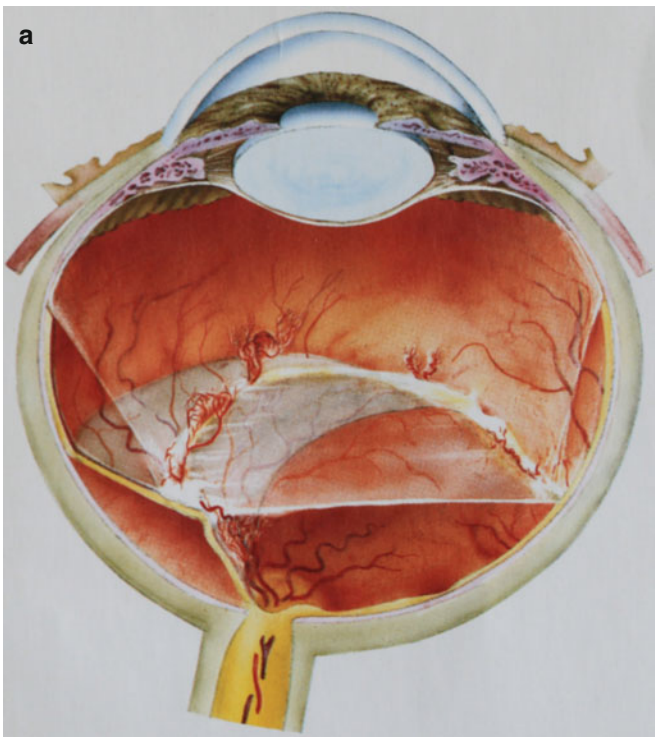

Figure III.L-6 *PDVR, stage B*: this (**a**) stage is characterized by shrinkage of the posterior vitreous cortex. In places where the vitreous adheres to the retina, circumscribed retinal detachments are found

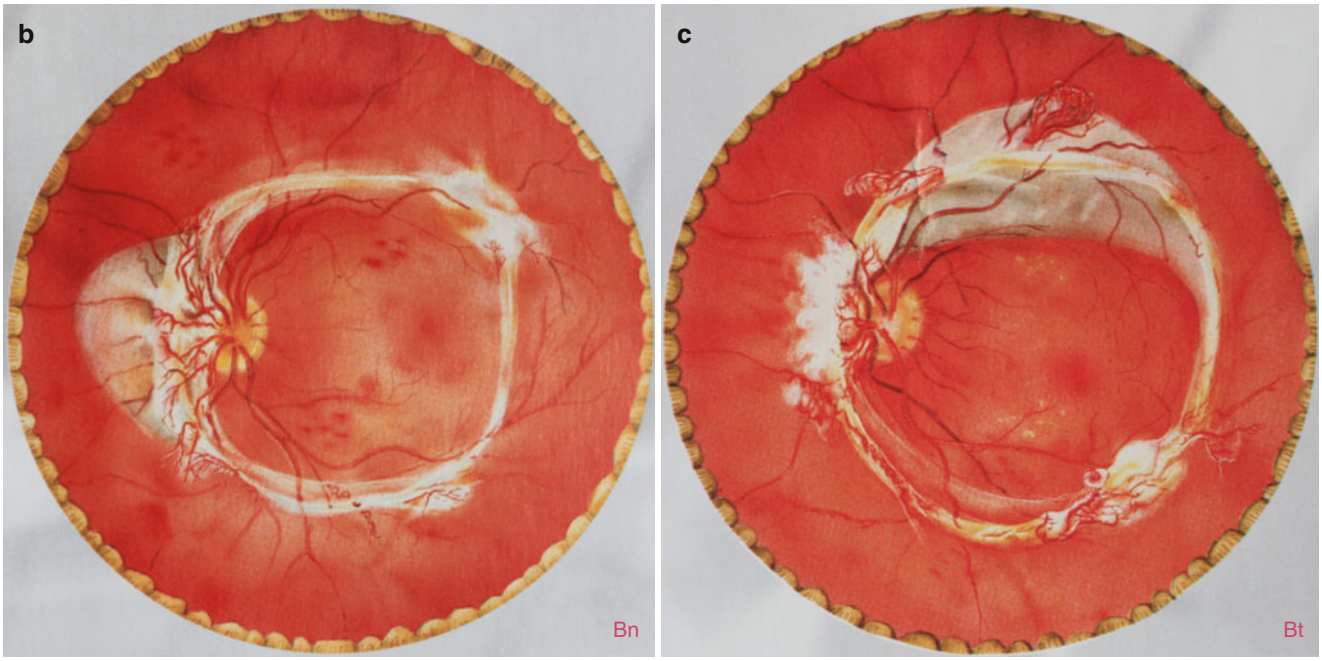

Figure III.L-6 (continued) (**b**) If a tractive detachment is *nasal* to the optic disc, this is described as stage Bn. (**c**) Proliferative and tractive changes in the area of the *temporal* superior and inferior vascular arcade, which may be followed by a macular detachment, are categorized as stage Bt

disk. Very important for the functional prognosis in this stage is the fact that the macula remains unaffected and the visual acuity, depending on additional diabetic changes in the macular area, may be normal.

Stage C (Figure III.L-7a–e): Increased shrinkage of vitreous induces vigorous traction leading to traction retinal detachment. With further progression, the macula becomes involved. Corresponding with the four quadrants of the fundus, this stage is divided into four subgroups: *stage C 1*, traction RD in one quadrant; *stage C 2*, traction RD in two quadrants; *stage 3*, traction RD in three quadrants; and *stage 4*, traction RD in all 4 quadrants. In stage C, visual acuity is dramatically decreased, since in all cases the macula is involved. In all stages, additional hemorrhages may occur, since vitreous traction can also rupture proliferating blood vessels.

III. Therapeutic Considerations

In a retrospective review of 563 patients, Hesse et al. [15] evaluated the prognostic value of Kroll's classification with respect to the postoperative visual outcome after vitreoretinal surgery. In 179 out of 563 eyes (31.7 %), repeat vitrectomy (including silicone oil removal) was required, and in 51 eyes (9.1 %), more than one reoperation was performed. Silicone oil tamponade was used in 22 out of 253 eyes (8.7 %) classified as *stage A*, in 27 out of 201 eyes (13.4 %) of *stage B*, and in 17 out of 78 eyes (21.8 %) of *stage C*. The mean postoperative visual acuity after vitreoretinal surgery was significantly better in *stage A* compared to *stage C* ($p<0.01$). Postoperative increase of visual acuity of more than 3 lines was significantly less frequent in *stage B* ($p<0.014$) and *stage C* ($p<0.039$) as compared to *stage A*. The authors concluded that Kroll's classification for PDVR has a high prognostic value for postoperative visual outcome and the level of surgical risk management.

All of these clinical observations and experimental investigations point to the fact that the vitreous plays a key role in the development of a PVDR [6]. Therapeutic aims must therefore either prevent diabetic vitreopathy or eliminate vitreoretinal adhesion. As long as the retina is still attached, PRP may be effective if PVD can be achieved. However, PRP cannot often be administered early enough in the natural history of PDVR, and in other cases, PRP is simply not effective due to robust vitreoretinal adhesion and traction. In the presence of vitreous hemorrhage and traction retinal detachment, only the surgical release of traction via vitrectomy can save the diabetic eye. In recent years, the option of inducing PVD via pharmacologic vitreolysis [48, 49, 51, 56, 61, 64] has become available [see chapter VI.A. Pharmacologic vitreolysis]. A recent review outlines how pharmacologic vitreolysis can be used to treat diabetic retinopathy [6].

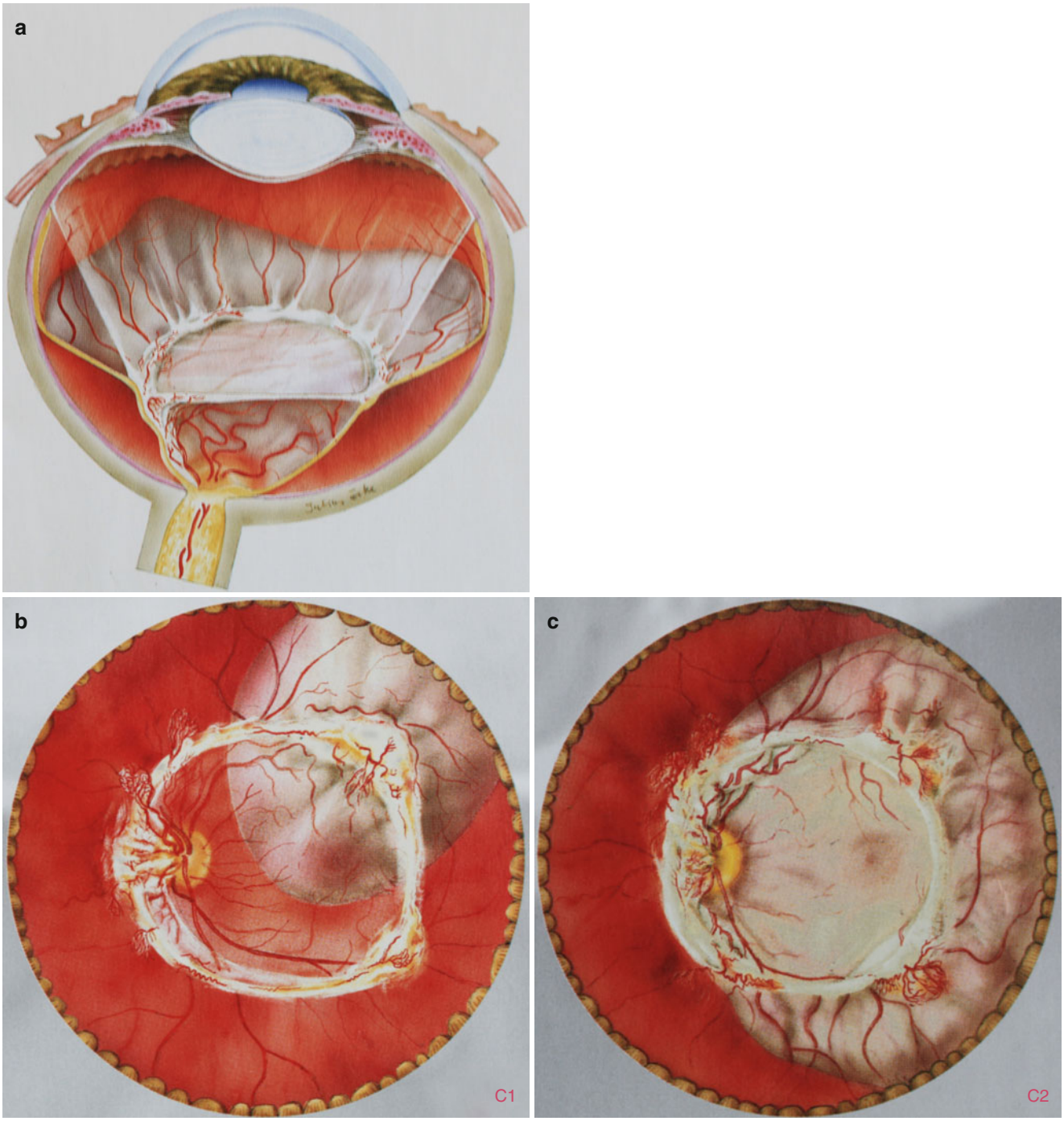

Figure III.L-7 (**a**–**e**) PDVR, stage C. Stage C is – similarly to the PVR classification – characterized by a traction retinal detachment, which includes the macula. PDVR, stage C. According to the number of quadrants involved, stages C1–C4 are distinguished

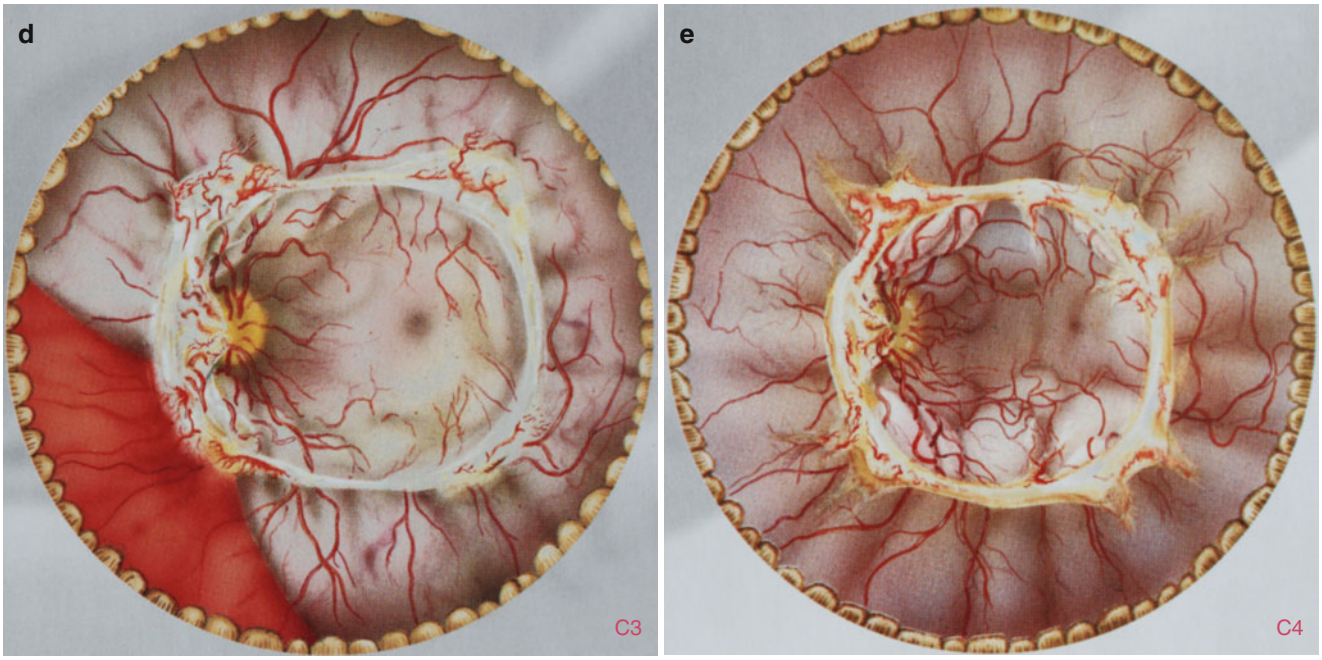

Figure III.L-7 (continued)

IV. Summary

While the underlying pathogenesis of NPDR has a multifactorial origin consisting of intraluminal and extraluminal factors of the retinal vessels and biochemical components of growth factors and especially advanced glycation end products, PDVR appears to reflect a different etiology. The vitreoretinal interface, especially the posterior vitreous cortex, plays a key role in the pathogenesis of PDVR. This vitreoretinal interface is thickened tenfold and becomes a metabolic barrier between retina and vitreous, leading to an accumulation of VEGF, expressed mainly by the Müller cells, which explains the proliferation of pathologic new vessels out of the retina into the posterior vitreous cortex. With progression toward PDVR, shrinkage of the posterior vitreous cortex with its tight adhesions to the retina results in the dramatic changes of traction retinal detachment. The classification for NPDR, established by the ETDRS in 1981 [7], has been confirmed by the International Clinical Diabetic Retinopathy Severity Scale in 2003. However, these classifications did not consider the role of diabetic vitreopathy [see chapter I.E. Diabetic vitreopathy] in the course of the proliferating forms of diabetic retinopathy and the status of the vitreoretinal interface [16]. Therefore, a morphological classification has been established, which combines the severity of the retinopathy with the status of diabetic vitreopathy. For this reason, the accurate and more precise term PDVR should be used instead of the more generalized term PDR. This classification system serves:

1. To document morphological fundus changes in PDVR
2. To grade the severity of the PDVR
3. To improve communication between ophthalmologists as well as patients
4. To indicate all forms of therapy: laser treatments, as long as the retina is attached; pars plana vitrectomy for removal of tractional vitreous, hemorrhages and attach the retina; and probably in the near future pharmacologic vitreolysis treatments
5. To predict the success of any treatment
6. To predict the further course of the diabetic fundus changes
7. To serve for retro- and prospective studies of any outcome of treatments or other defined studies of diabetic retinopathy

Abbreviations

AAO	American Academy of Ophthalmology
DCCT	Diabetes Control and Complication Trial
DM	Diabetes mellitus
DR	Diabetic retinopathy
DRVS	Diabetic Retinopathy Vitrectomy Study
EGF	Endothelial growth factor
ETDRS	Early Treatment Diabetic Retinopathy Study
ICDRS	International Clinical Diabetic Retinopathy Severity
ILM	Inner limiting membrane

IRMAs	Intraretinal microvascular abnormities
NPDR	Nonproliferative diabetic retinopathy
PDGF	Platelet-derived growth factor
PDR	Proliferative diabetic retinopathy
PDVR	Proliferative diabetic vitreoretinopathy
PRP	Panretinal laser photocoagulation
PVD	Posterior vitreous detachment
PVR	Proliferative vitreoretinopathy
RD	Retinal detachment
TGF	Transforming growth factor
IL-1	Interleukin 1
UKPDS	United Kingdom Prospective Diabetes Study
VEGF	Vascular endothelial growth factor
WESDR	Wisconsin Epidemical Study of Diabetic Retinopathy

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