Posterior Vitreomacular Adhesion: A Potential Risk Factor for Exudative Age-related Macular Degeneration?

ILSE KREBS, WERNER BRANNATH, CARL GLITTENBERG, FLORIAN ZEILER, JERRY SEBAG, AND SUSANNE BINDER

• PURPOSE: **To compare the state of the posterior vitreous in exudative age-related macular degeneration (AMD) with eyes with nonexudative AMD and controls.**
• DESIGN: **Prospective, observational case series.**
• METHODS: **B-scan ultrasonography and optical coherence tomography (OCT) were performed in 163 eyes from 82 subjects older than 55 years, 50 eyes with exudative AMD, 57 with nonexudative AMD, and 56 control eyes. Main outcome measures were the number of eyes with complete posterior vitreous detachment (PVD) by ultrasound and the number of eyes with central vitreomacular adhesion by OCT.**
• RESULTS: **By ultrasonography, 17 (34.0%) of 50 eyes with exudative AMD had PVD as compared with 41 (71.9%) of 57 eyes with nonexudative AMD (P = .00002) and 34 (60.7%) of 56 controls (P = .017). OCT detected persistent central vitreoretinal adhesion surrounded by a detached posterior vitreous cortex in 18 (36%) of 50 eyes with exudative AMD, significantly higher than in nonexudative AMD (4/57 [7%]; P < .0001) and in controls (6/56 [10%]; P = .002).**
• CONCLUSIONS: **Persistent attachment of the posterior vitreous cortex to the macula may be another risk factor for the development of exudative AMD via vitreoretinal traction inducing chronic low-grade inflammation, by maintaining macular exposure to cytokines or free radicals in the vitreous gel, or by interfering in transvitreous oxygenation and nutrition of the macula. Inducing PVD may provide prophylactic benefit against exudative AMD. (Am J Ophthalmol 2007;144:741–746.**

THE CAUSE OF EXUDATIVE AGE-RELATED MACULAR degeneration (AMD) is not fully understood. Genetic factors, oxidative stress, ischemia, aging of the retinal pigment epithelium, and inflammation are proposed etiologic factors.[1] Although vitreous has been studied extensively for other macular diseases like macular holes,[2–4] and although the profound molecular and structural changes within the aging vitreous are known,[5–7] the role of the vitreoretinal interface has not yet been examined sufficiently in the context of AMD. Prior studies using ultrasonography have found a higher incidence of attached posterior vitreous in AMD,[8,9] but there was no difference noted between nonexudative and exudative forms. The studies presented herein used both ultrasound and optical coherence tomography (OCT) to characterize the relationship between the posterior vitreous and the macula in subjects with both forms of AMD as well as age-matched controls.

METHODS

IN THIS PROSPECTIVE, COMPARATIVE STUDY, ONLY PAtients 55 years of age or older were enrolled. Both eyes of a patient were included. Sufficient visualization of the retina by physical examination was required to provide useful quality for fluorescein angiography (FA) and OCT evaluation of the posterior segment. Eyes with evidence of neovascular AMD in FA were included in group 1 (exudative AMD), eyes with either pigmentary changes or drusen were included in group 2 (nonexudative AMD), and eyes without abnormalities of the macula were included in group 3 (control). If both eyes of a patient could be included, they were assigned independently to one of the three groups. Special attention was paid to exclude diseases affecting the vitreous like diabetic retinopathy, macular pucker, inflammatory diseases, macular holes, myopia of more than 2 diopters, and synchisis scintillans, even when combined with AMD.

Assignment to the subgroups (nonexudative AMD, exudative AMD, and controls) was performed according to the results of posterior segment biomicroscopy and FA with the Heidelberg Retina Angiograph (Heidelberg Engineering, Heidelberg, Germany). Eyes in the nonexudative group were classified further according to the Age-Related Eye Disease Study (AREDS) classification system:[10,11] AREDS III, high risk to develop neovascular AMD; AREDS II, medium risk; AREDS I, low risk; AREDS IV, geographic atrophy, lowest risk.

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From the Ludwig Boltzmann Institute for Retinology and Biomicroscopic Laser Surgery, Vienna, Austria (I.K., S.B.); the Department of Ophthalmology, Rudolph Foundation Clinic, Vienna, Austria (I.K., C.G., F.Z., S.B.); the Core Unit for Medical Statistics and Informatics, Medical University, Vienna, Austria (W.B.); and the VMR Institute, Huntington Beach, and the Department of Ophthalmology, University of Southern California, Los Angeles, California (J.S.).
Inquiries to Ilse Krebs, Department of Ophthalmology, Rudolf Foundation Clinic, Juchgasse 25, 1030 Vienna, Austria; e-mail: Ilse.Krebs@wienkav.at

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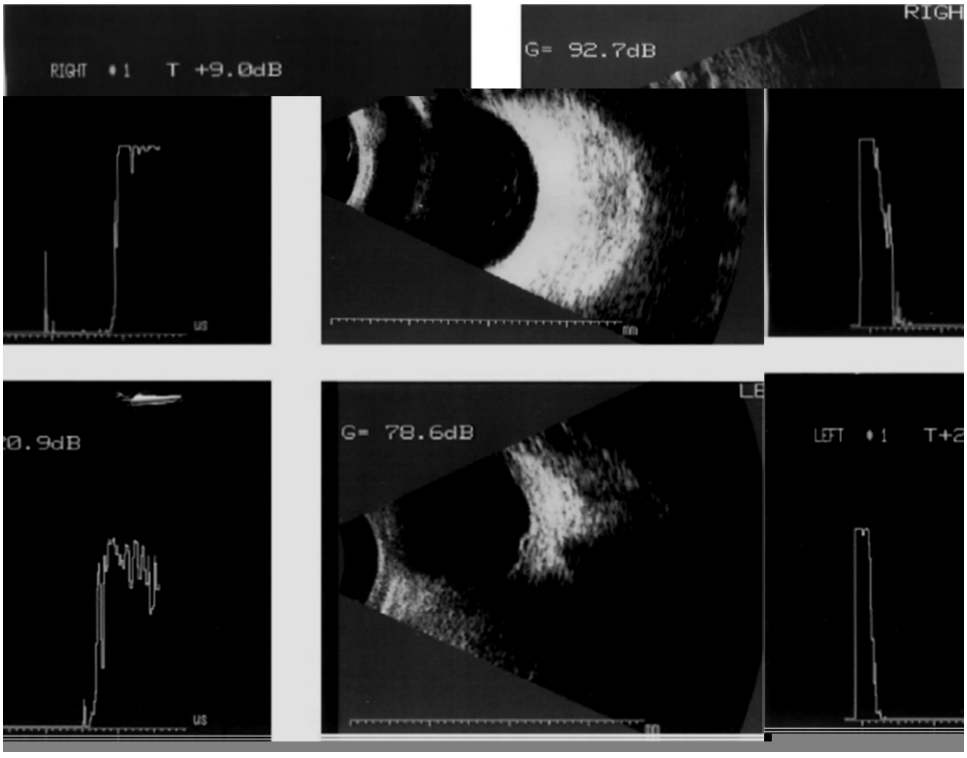

FIGURE 1. A-scan and B-scan ultrasonography images demonstrating detached and attached vitreous cortex. (Top) The posterior vitreous cortex is detached in an eye with nonexudative age-related macular degeneration (AMD), a single peak of moderate reflectivity in the vitreous cavity is seen in (Left) the A-scan image, corresponding to (Right) a line in the B-scan image. (Bottom) The posterior vitreous cortex is attached, without any echoes detected in the vitreous cavity, either on (Left) the A-scan image or (Right) the B-scan image. A small elevation in both scans in front of the posterior pole corresponds with the neovascular lesion.

• **ULTRASONOGRAPHY:** Ultrasonography with a high-gain, real-time ultrasound device (10-MHz probe; BVI Biovision; B.V. International, Paris, France) was performed by independent experienced examiners not involved in the OCT examinations. A through-the-lid contact technique was used with a coronal probe position to avoid lens artifacts, as well as two central through-the-lens views. The mobility of the posterior vitreous was examined during ocular saccades. A-scan ultrasound complemented the B-scan ultrasound examination.

• **OPTICAL COHERENCE TOMOGRAPHY:** After mydriasis, OCT was performed with the Stratus III OCT Scanner (Carl Zeiss, San Leandro, California, USA). Scanning was performed using an internal fixation beam or an external fixation light for the fellow eye when internal fixation was not possible. When steady fixation was achieved, the center of the scans was positioned in the geometric center of the fovea. The intensity of the incident light was set to the maximum (750 μW) to detect even weak signals from the posterior vitreous cortex. Six radial scans through center of the fovea were performed with additional lines through the upper and lower arcades, as well as radial lines through the optic disk.

• **STATISTICAL ANALYSES:** The exudative AMD, nonexudative AMD, and control groups were compared with respect to the presence of a complete posterior vitreous detachment (PVD) and partial PVD by ultrasonography and the presence of central vitreomacular adhesion surrounded by localized vitreoretinal separation, determined by OCT. Because the outcome of patients with measurements from both eyes often are inhomogeneous between eyes, we analyzed all eyes and report percentage values for eyes instead of patients. The binary outcome variables, which were the primary end points, were analyzed using the generalized estimation equation approach, which accounts for the repeated measurements from some of the patients. In this approach, univariate and multivariate logistic regression analyses with robust variance estimates for contrasts were applied. The robust variance estimates were used because outcomes from eyes from the same subject may be correlated, and robust variance estimates account properly for such correlations.[12] Multivariate analyses included age and gender as additional covariates, and the differences between the three groups were tested by robust analyses of deviance and robust post hoc contrast tests. The statistical analyses were carried out using the design package for robust variance estimation, robust F, and Wald

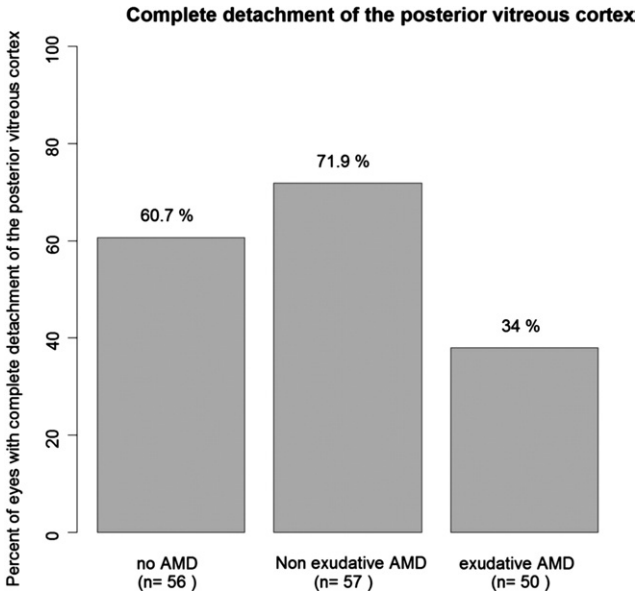

FIGURE 2. Bar graph demonstrating the frequency of posterior vitreous detachment (PVD) assessed with ultrasound separately for eyes with exudative AMD, nonexudative AMD, and without AMD. The box plots show that the frequency of PVD by ultrasound is statistically smaller in the group of exudative AMD patients compared with the group of patients with nonexudative AMD and the control group.

tests. *P* values of .05 or less were considered statistically significant.

RESULTS

• **DEMOGRAPHIC DATA:** In 163 eyes from 82 subjects older than 55 years of age, there were 50 eyes with exudative AMD, 57 with nonexudative AMD, and 56 control eyes. A total of 163 eyes in 82 subjects (one second eye could not be included because of subretinal surgery in that eye) were included. Sixty-one patients had the same pathologic features in both eyes (15 patients with exudative AMD, 21 patients with nonexudative AMD, and 25 controls), 14 patients had exudative AMD in one eye and nonexudative AMD in the fellow eye, and six patients had exudative AMD in one eye and no signs of AMD in the fellow eye.

In the entire study population, 33% of the patients were male and 67% were female, with a mean age ± standard deviation of 74 ± 7.0 years (range, 55 to 89 years); distribution of gender and age was similar in the subgroups.

Ten eyes (17.5%) were classified as AREDS III, 21 (36.8%) as AREDS II, and 22 eyes (38.6%) as AREDS I. The remaining four eyes (7.0%) had geographic atrophy. Twenty-five eyes (43.9%) with nonexudative AMD showed predominantly drusen and 32 (56.1%) primarily had pigmentary changes.

• **ULTRASONOGRAPHY:** Of the 50 eyes with exudative AMD, 17 (34%) had a complete PVD, as compared with 41 (71.9%) of 57 eyes with nonexudative AMD ($P = .00002$), and 34 (60.7%) of 56 control eyes ($P = .014$; Figures 1 and 2; Table). A partial PVD only in the peripheral vitreous was observed in 15 (30%) of 50 eyes with exudative AMD, as compared with seven (12.3%) of 56 eyes with nonexudative AMD ($P = .02$; Table) and three (5.4%) of 56 control eyes ($P = .003$; Table).

• **OPTICAL COHERENCE TOMOGRAPHY:** Partial PVD, seen on OCT as persistent adhesion in the central macula surrounded by a detached vitreous cortex (Figure 3), was detected in 18 (36%) of 50 eyes with exudative AMD, as compared with four (7%) of 57 eyes with nonexudative AMD ($P < .0001$) and six (11%) of 56 control eyes ($P = .002$; Figure 4). The location of the persistent adhesion was always in the foveal region non-exudative and control eyes. In the exudative AMD group it was in the fovea in 15/50 eyes, all of them with subfoveal CNV. In the three exudative group eyes with juxtafoveal neovascular lesions, the adhesion also was juxtafoveal over the area of the CNV. In the four nonexudative and six control eyes, persistent central adhesion was in the fovea. Logistic regression analyses (Table) confirm that central vitreomacular adhesion surrounded by elevation of the posterior vitreous cortex is significantly (statistically) more frequent in the group of eyes with exudative AMD than in the group of eyes with nonexudative AMD and the control group.

DISCUSSION

VITREOUS CHANGES DURING AGING HAVE BEEN DESCRIBED by Foos[13] and Sebag.[5–7] Age-related vitreous liquefaction in conjunction with weakening of vitreoretinal adhesion[7] result in PVD. The incidence of PVD increases with age[13] so that by the eighth decade, the risk of PVD was reported to be approximately 63%.[13] However, our own observations during vitrectomy and submacular surgery in 66 eyes with exudative AMD (mean age, 77.8 years) showed that in 55 (83%) of 66 eyes, there was an attached posterior vitreous cortex.[14] Indeed, a previous study with ultrasound in patients with AMD showed a lower incidence of PVD (33%) than in an age-matched control group without AMD (50%), but the differences between exudative and nonexudative AMD were not significant.[8] Large studies have verified cigarette smoking, hereditary factors, large drusen, and pigmentary changes as risk factor for severe AMD.[15–18] Studies conducted on twins showed a high concordance of the phenotype of AMD more impressive in monozygotic twins, confirming a genetic influence in AMD.[19–21] However, differences in phenotype and grading of AMD in both eyes cannot be explained by environmental and genetic factors alone. In our study, 24.4% of

TABLE. Logistic Regression Analysis of Posterior Vitreous Detachment

	Complete PVD				Partial (Peripheral) PVD				Persistent Adhesion in the Central Macula on OCT			
	Odds Ratio	Lower Limit	Upper Limit	*P* value	Odds Ratio	Lower Limit	Upper Limit	*P* value	Odds Ratio	Lower Limit	Upper Limit	*P* value
Nonexudative vs exudative AMD	6.23	2.35	16.52	.0002	0.310	0.117	0.819	.02	0.11	0.04	0.34	.0001
Control vs exudative AMD	3.97	1.32	11.91	.014	0.132	0.034	0.512	.003	0.15	0.05	0.50	.002
Nonexudative vs control	1.57	0.56	4.43	.4	2.35	0.58	9.46	.2	0.76	0.17	3.45	.7

AMD = age-related macular degeneration; OCT = optical coherence tomography; PVD = posterior vitreous detachment. Contrasts are given in terms of odds ratios.

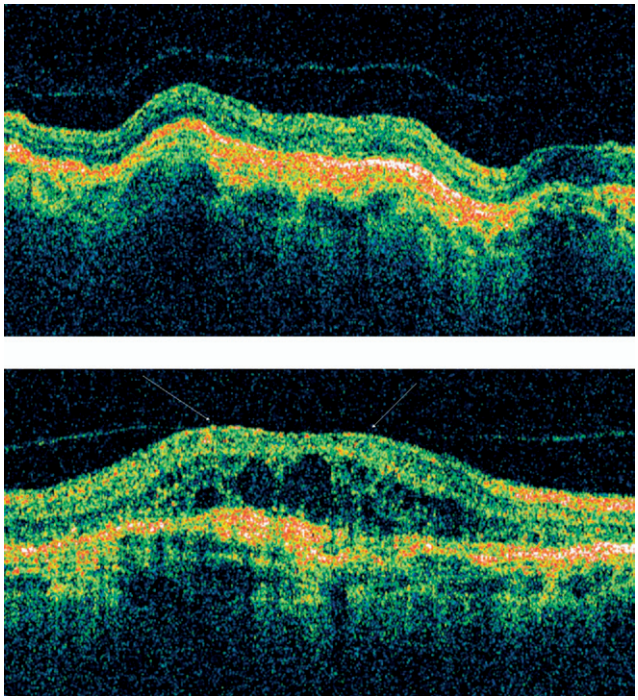

FIGURE 3. Optical coherence tomography (OCT) images demonstrating the position of the posterior hyaloid. (Top) Shallow detachment of the posterior vitreous cortex in front of the lesion without any adhesion to the retina surface in a case of nonexudative AMD. Corresponding to the geographic atrophy, the pigment epithelium and choriocapillaris band are thickened and the penetration into the tissue is enhanced. (Bottom) The posterior vitreous cortex (arrows) is attached in the area of the neovascular lesion (cystic edema, irregularly thickened and interrupted band corresponding to the pigment epithelium and choriocapillaris layer) surrounded by a shallow vitreoretinal separation.

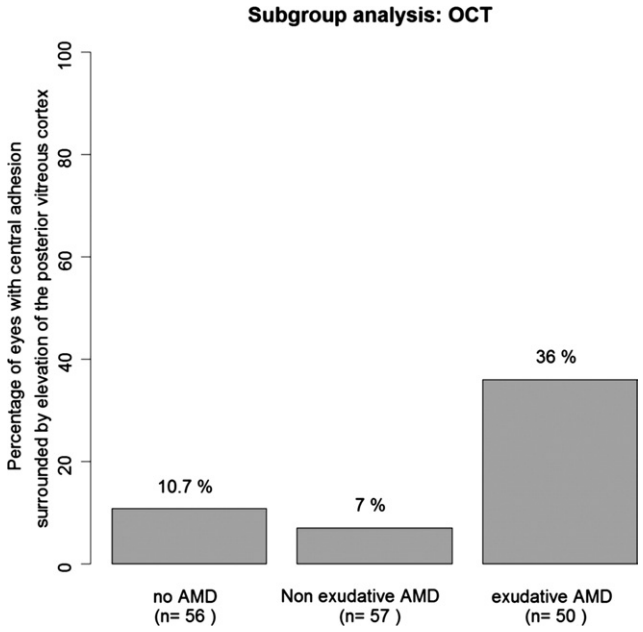

FIGURE 4. Bar graph demonstrating the frequency of adhesion of the posterior vitreous in the area of the neovascularization surrounded by a shallow vitreoretinal separation assessed with OCT separately for eyes with exudative AMD, nonexudative AMD, and without AMD. The box plots show a significantly higher incidence in exudative AMD group compared with nonexudative AMD and the control groups.

the patients had exudative AMD in only one eye and no sign of AMD or nonexudative AMD in the fellow eye. Additional ocular conditions, including the position of the posterior vitreous cortex, may be responsible for these differences, besides time-related differences of disease onset.

In the present study, there is a significantly higher prevalence of complete PVD in eyes with nonexudative AMD (72%) and controls (61%), as compared with eyes with exudative AMD (34%). That this study detected differences that were not identified previously may be explained by the use of high-resolution ultrasound, making the identification of the posterior vitreous cortex and PVD easier and more accurate. Furthermore, in the previous studies, there was no information concerning the type and severity of AMD. In our study, there was a clear-cut difference in severity of AMD between nonexudative and exudative groups, with only 17.5% of the nonexudative group classified as AREDS III (high risk for exudative

AMD) and all eyes in the exudative AMD group demonstrating clear-cut evidence of choroidal neovascularization. The findings on ultrasound were supplemented by OCT studies where partial PVD, defined as central vitreoretinal adhesion surrounded by a shallow detachment of the posterior vitreous cortex, was identified far more frequently in exudative AMD. More specifically, the attachment site of vitreous to the macula corresponded to the location of choroidal neovascularization (i.e., in juxtafoveal neovascularization, vitreoretinal adhesion was juxtafoveal as well), further suggesting a causal relationship.

Sebag[22] recently proposed the concept of anomalous PVD where gel vitreous liquefaction without concurrent vitreoretinal dehiscence exerts traction on the retina where vitreous remains adherent. This unifying concept of vitreoretinal diseases postulates that this pathogenic mechanism is the initiating event in diseases such as retinal tears and detachments, macular holes and pucker, and advanced proliferative diabetic vitreoretinopathy. The results of the study presented herein suggest that in eyes with AMD, anomalous PVD could be a significant risk factor for progression from nonexudative to exudative forms of AMD. This could occur via the effects of vitreomacular adherence in one or more of three ways:

1) Anomalous PVD with persistent vitreomacular adherence could induce chronic, low-grade inflammation in the macular region. Several lines of investigation have led to the opinion that inflammation plays an important role in early as well as late stages of AMD.[23–25]

2) Another possible disease mechanism is that the presence of an attached posterior vitreous prevents the normal diffusion of oxygen and nutrients required by the metabolically active cells of the macula, if there is abnormal tissue at the vitreomacular interface. Indeed, Sebag and Hageman[26] emphasized that there are many embryologic, molecular, and structural similarities between the Bruch membrane and the internal limiting lamina of the retina, and thus it is likely that the combined effects of genetics, chronic inflammation, and aging are similar at these two interfaces.

3) A third possibility is that the presence of an attached posterior vitreous confines proangiogenic cytokines in the macula, contributing to choroidal neovascularization. The important role of vascular endothelial growth factor (VEGF) and other cytokines in the pathogenesis of exudative AMD has been described previously.[27] Bishop and associates reported alterations in vitreous collagen fibrils during aging and argued that VEGF may be bound by these altered collagen fibrils at the interface between retina and the posterior vitreous cortex.[28] Because of persistent attachment of the posterior vitreous to the macula, there could be more intense macular exposure to these cytokines, contributing to neovascularization and exudative AMD.

There may be more similarities between the vitreoretinopathy of diabetes and AMD than appreciated previously. It is known that advanced glycation end-products in diabetic vitreopathy[29] alter vitreous biochemistry[30] and structure.[31] Advanced glycation end-products also are present in aging (nondiabetic) vitreous collagen,[32] and thus one may speculate that similar mechanisms at the vitreomacular interface may contribute to both diabetic vitreoretinopathy and exudative AMD. It is known that complete PVD is associated with a very low incidence of neovascularization in diabetes, whereas partial PVD is a significant risk factor for vascular proliferation.[33] The OCT findings in the study presented herein that a localized vitreous adhesion is associated with a high incidence of choroidal neovascularization suggests that there may be similar underlying causes at play in both diabetes and AMD. However, the exact contribution of vitreoretinal adhesion in the macula remains uncertain, and future investigations should explore the exact nature of these events as well as the advisability of using pharmacologic vitreolysis[34–36] to induce a PVD as prophylaxis against exudative AMD.

Compared with large epidemiologic studies examining risk factors of severe AMD like cigarette smoking, hereditary factors, large drusen, and pigmentary changes,[15–18] the number of participants was small in the current study. However, even in this small group, we found a significant correlation between vitreoretinal adhesion and exudative AMD. Further studies with more participants observed longitudinally over a longer period and evaluated by more advanced imaging systems (ultrasound and high-resolution/spectral-domain OCT systems) are required to validate our observations about the importance of vitreoretinal adhesion as a potential risk factor for exudative AMD. It is necessary to determine whether an attached posterior vitreous cortex is indeed a pathogenic factor or whether there is only an association of exudative AMD and attached posterior cortex. Furthermore, by correlating the findings with other known risk factors, future studies may help elucidate which of the several theories proposed above may explain the observations of this study.

In conclusion, OCT and ultrasound evaluations were used to identify the exact location of the posterior vitreous in relation to the macula. The combination of these two tests has shown that in exudative AMD, the posterior vitreous cortex is attached more frequently than in nonexudative AMD and in controls. The detection by OCT of a partial PVD with vitreous adhesion in the area of the neovascularization and a surrounding shallow vitreous detachment suggests that in similar fashion to diabetic retinopathy, a partial PVD is a significant risk factor for exudative AMD.

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S.B.); final approval of the article (I.K., W.B., J.S., S.B.); data collection (C.G., F.Z.); statistics (W.B.); literature search (I.K., C.G., F.Z., J.S.); and administrative support (C.G., F.Z.). Institutional review board approval and complete informed patient consent were obtained for all patients. Data collection was in compliance with the tenets of the Declaration of Helsinki.

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Biosketch

Ilse Krebs, MD, received her medical degree from the Vienna Medical University. Since 1986, she is senior physician at the Department of Ophthalmology, Rudolf Foundation Clinic in Vienna and since 1997, vice chairman of the Department of Ophthalmology, Rudolf Foundation Clinic. Dr Krebs areas of research interest are diagnosis and therapy of macular diseases including photodynamic therapy, anti-VEGF therapy, fluorescein angiography, optical coherence tomography, and she has published a series of articles concerning these topics.