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Posterior vitreous detachment following panretinal laser photocoagulation*

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Abstract. A total of 30 eyes of 19 patients with type I diabetes, varying severity of retinopathy, and no posterior vitreous detachment (PVD) were studied clinically, and vitreous examination was performed by preset lens biomicroscopy. Follow-up was 4.0–7.5 years. A total of 15 eyes underwent panretinal laser photocoagulation (PRP) and 15 eyes were left untreated. The incidence of PVD was 8 of 15 (53%) after PRP and 1 of 15 (7%) in untreated eyes ($P < 0.02$). Minimal vitreous hemorrhage occurred in 4 of 7 treated eyes (57%) that did not develop PVD and in only 2 of 8 (25%) that did. In treated eyes with no history of vitreous hemorrhage, the incidence of PVD was 6/9 (67%); in treated eyes with minimal vitreous hemorrhage at any time, it was 2/6 (33%). In treated eyes, the presence of Diabetic Retinopathy Study (DRS) high-risk characteristics was equally frequent in eyes that developed PVD as in those that did not. These data suggest that PVD occurs following PRP, independent of the severity of diabetic retinopathy or prior vitreous hemorrhage.

Introduction

Panretinal laser photocoagulation (PRP) has become a mainstay in the treatment of proliferative diabetic retinopathy (PDR). The Diabetic Retinopathy Study (DRS) [8], an optimally controlled prospective investigation, demonstrated conclusively that PRP reduces the risk of severe visual loss in patients with high-risk characteristics [neovascularization of the disc (NVD) greater than standard photograph 10A or neovascularization elsewhere (NVE) with vitreous hemorrhage]. The exact mechanism that produces this effect is still unknown.

Histopathologic studies [9] have shown that in PDR, new vessels grow directly into the vitreous cortex, providing a "scaffold" for fibrovascular proliferation. The role of the vitreous in PDR has been further elucidated by photographic documentation of the vitreoretinal interface using preset lens biomicroscopy [15, 24, 26]. These studies have demonstrated that little or no progression of retinopathy occurs in eyes with complete posterior vitreous detachment (PVD). Eyes with partial PVD and persistent traction from vitreous attached to the neovascular complexes show progression of diabetic retinopathy in over 50% of cases. Furthermore, eyes with PDR and partial PVD that subsequently develop complete PVD show regression of new blood vessels [7]. Therefore, the development of complete vitreous detachment has a salutary effect on the course of PDR.

To date it has not been possible to evaluate experimentally the role of the vitreous in PDR, owing to the absence of an adequate animal model. Clinical studies of the natural history of PDR and the effects of laser photocoagulation therapy are difficult to justify, inasmuch as it is unethical to withhold PRP in patients with at least high-risk characteristics as derived by the DRS; therefore, a proper control group can no longer be assembled for a study of the various effects of PRP. Insight into the pathophysiology and response to treatment can nonetheless be obtained through careful clinical correlation and documentation of findings.

The present study monitored the evolution of vitreous detachment in a group of type I diabetic patients, some of whom underwent laser treatment for PDR. The vitreous was examined on multiple occasions and the findings were documented photographically using preset lens biomicroscopy. Use of the El Bayadi-Kajiura lens enabled the observation of subtle vitreoretinal relationships that might not be seen with the Goldmann lens [2]. To minimize the influence of aging changes on the vitreous, only young patients were studied. In an effort to explain the therapeutic effect of laser treatment in patients with PDR, this prospective study assessed the state of the vitreoretinal interface following PRP. The objective was to determine whether a relationship exists between PRP and the development of PVD.

Patients and methods

A total of 142 patients with diabetic retinopathy, aged 33 years or younger, seen at the Retina Associates in Boston between 1979 and 1986 were randomly selected by chart review as the database. Exclusion criteria were the presence of vitreous hemorrhage greater than grade V_1 (where >2/12 of the fundus area is obscured) according to the Lee classification [17] at any time prior to or during the study, a history of trauma or intraocular surgery at any time prior to or during the study, other vitreoretinal disease, or prior laser

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Table 1. Patient population

	PRP ($n=15$ eyes)	No PRP ($n=15$ eyes)
Mean age at study entry (years)	27.1 (range, 21–33)	27.3 (range, 14–33)
Mean duration of diabetes at study entry (years)	18.6 (range, 11–25)	16.1 (range, 1–28)
Mean follow-up (years)	4.0	4.5
Incidence of PVD	8/15 (53%)*	1/15 (7%)*
Age at PVD (years)	26 (range, 21–30)	34 ($n=1$)

* Difference significant at the $P<0.02$ level

Table 2. Clinical profile of 15 eyes treated with PRP

Patient number	Age at entry (years)	Sex	Duration of diabetes at entry (years)	Minimal vitreous hemorrhage[a]	DRS high risk	Type	Number of PRP applications	Partial PVD	Total PVD
1	21	F	15	−	+	NVD	3700	+	
2	25	M	19	−	+	NVD, NVE	4000		+
3	30	M	17	−	−	−	900	+	
4 OD	24	F	11	+	+	NVD, VH	2100		+
OS				+	+	NVD, NVE, VH	2984		+
5	28	F	25	−	+	NVD, NVE	1700	+	
6	27	M	23	−	+	NVD, NVE	2586		+
7	21	M	15	−	+	NVD	1800	+	
8	31	F	23	−	−	NVE	1800		
9 OD	28	M	20	+	+	NVE, VH	1702		
OS				+	+	NVD, NVE, VH	2037		
10	33	M	16	+	+	NVE, VH	2033	No PVD	
11	21	M	15	+	+	NVE, VH	1007		
12 OD	33	F	25	−	−	−	1500		
OS				−	−	NVE	1600		

[a] Minimal vitreous hemorrhage designates grade V_1 or less (Lee classification [17])

NVD, neovascularization of the disk; NVE, retinal neovascularization; DRS, Diabetic Retinopathy Study; VH, vitreous hemorrhage; +, present; −, absent. Patients 3, 8, and 12 (OD) did not have high-risk characteristics but received PRP because of advanced preproliferative changes (cotton wool spots, widespread capillary nonperfusion in patients 3 and 12 (OD), and NVE that looked ominous in patient 8)

therapy. Only eyes that were documented as having no PVD were entered in the study.

In all, 30 eyes of 19 patients (10 men and 9 women) met the above criteria. A total of 15 eyes in 11 patients underwent PRP treatment using an argon green laser with a 500-μm spot size, 0.2-s duration, and power settings sufficient to achieve a gray-white spot. Another 15 eyes with retinopathy displaying less than high-risk characteristics were not treated and served as controls. The two groups were otherwise comparable in age at study entry, in duration of diabetes, and in follow-up (Table 1). The mean follow-up was 4.0 years for PRP-treated patients and 4.5 years for untreated patients.

After standard pupil dilation, vitreous examination was carried out and documented photographically using a fundus camera and an aspheric +58.6 diopter preset lens, as previously described [25].

Results

No eye had PVD prior to PRP treatment. After PRP, PVD occurred in 8 of the 15 treated eyes (53%); only 1 of the 15 untreated eyes (7%) developed PVD during the study. This difference was significant at the $P<0.02$ level.

No eyes with vitreous hemorrhage at any time greater than grade V_1 were included in the study. Of the 15 treated eyes, 6 showed evidence of minimal vitreous hemorrhage ($\leq$ grade V_1) at some time during the investigation; 2 of these 6 eyes (33%) developed PVD following PRP and 4 (67%) did not (Table 2), suggesting that the occurrence of vitreous hemorrhage did not play a role in the subsequent development of PVD. Furthermore, of the 9 treated eyes that never showed evidence of vitreous hemorrhage, 6 (67%) developed PVD after PRP. Of the treated eyes that developed PVD, 2 of 8 (25%) displayed evidence of minimal vitreous hemorrhage at some time during their course.

Neovascularization of the disk or elsewhere was observed in 7 of 8 (88%) of the treated eyes that developed PVD and in 6 of 7 (86%) of the treated eyes that did not (Table 2). This suggests that the presence of neovascularization did not correlate with the subsequent development of PVD.

The mean number of laser applications was 2471 ± 1054 in eyes that developed PVD and 1668 ± 355 in eyes that did not; the difference had a P value of 0.08. PVD occurred in 3 of 8 (38%) eyes that received <2000 laser applications and in 5 of 7 (71%) eyes that received >2000 applications.

In 4 of 8 treated eyes that developed PVD, vitreous detachment was partial (Table 2). In the remaining 4 eyes, PVD was total in 1; nearly total, with persistent attachment to the disk, in 2; and partial, with attachment to a site of retinal neovascularization, in 1. Of the 4 eyes with partial PVD, 3 received <2000 laser applications (mean, 1467 ± 493), whereas all eyes with total or nearly total PVD received >2000 burns (mean, 2918 ± 807).

Discussion

It has been hypothesized that PRP destroys compromised tissue, thereby decreasing the amount of possible angiogenic factor(s) [6, 21] purportedly released from ischemic retina [16]. Experimental evidence [27] suggests that PRP destroys the metabolically active outer retina, decreasing O_2 consumption at this level and enabling the permeation of more O_2 from the choriocapillaris to the inner retina. In this manner, PRP reduces ischemia in diabetic retinopathy and possibly lessens the stimulus for neovascularization. It has also been hypothesized [11] that chorioretinal scars created by laser photocoagulation release a factor that inhibits angiogenesis. The progression of diabetic retinopathy may also be prevented by the development of PVD [15].

The results of our study suggest a relationship between PRP laser therapy and the subsequent development of PVD. The study population was selected so as to minimize the influence of age on PVD. The fact that no patients were older than 38 years of age at the completion of the study effectively rules out the possibility that PVD occurred as a consequence of aging changes in the vitreous [19]. PVD developed in 53% of PRP-treated eyes and in only 7% of untreated eyes.

The treated and untreated groups in this study were comparable in every respect except for the severity of diabetic retinopathy. Under ideal circumstances, this study should have randomized patients with respect to retinopathy in the treated and untreated groups; however, it would have been unethical to withhold PRP therapy in patients with "treatable" retinopathy (high risk).

Inasmuch as in this study PVD occurred in patients with high-risk characteristics necessitating laser treatment, factors such as vitreous hemorrhage and neovascularization could have influenced the development of PVD. However, there was no correlation between the presence of high-risk characteristics and the development of PVD in our treated patients. Although the presence of blood within the vitreous is known to induce liquefaction of the vitreous gel [1], this is a necessary but not sufficient element in the pathogenesis of PVD [19]. Thus, on the basis of available data, the development of PVD could not be attributed to vitreous hemorrhage. Leakage of serum proteins and enzymes from new blood vessels [4, 5] can induce vitreous liquefaction and perhaps even alter the strength of vitreoretinal adhesion. The higher incidence of PVD in the PRP-treated group may therefore have been due to leakage from new blood vessels; these vessels have abnormal endothelial tight junctions that could permit leakage. However, the prevalence of neovascularization in treated eyes was 88% in those that developed PVD and 86% in those that did not.

It could be argued that the higher incidence of NVD in the treated group that developed PVD as compared with the group that did not (Table 2) accounts for the 53% incidence of PVD following PRP. However, two points are noted against this postulate. First, there is no evidence to suggest that serum leakage from new vessels at the disk is greater than that from new vessels in the retina. In fact, one clinical study [5] showed no statistically significant difference between vitreous fluorophotometry readings in diabetic patients with NVD and those with NVE ($0.1 > P > 0.05$). This suggests that leakage from new vessels on the disk is equivalent to that from new retinal vessels in terms of influencing vitreous liquefaction and detachment. The incidence of NVD and NVE was the same in the treated group that developed PVD as in the treated group that did not (Table 2).

Second, it is revealing to consider the Diabetic Retinopathy Study (DRS) high-risk characteristics of the 15 eyes that received PRP treatment (Table 2). High-risk characteristics were present in 7 of 8 (88%) eyes that developed PVD and 4 of 7 (57%) eyes that did not. All 4 eyes in the latter group had minimal vitreous hemorrhage, which introduced large amounts of serum proteins and enzymes into the vitreous body, yet PVD did not develop in any of these eyes. This suggests that the presence of DRS high-risk characteristics such as NVD or vitreous hemorrhage cannot explain the increased incidence of PVD observed following PRP.

Thus, the results of this study suggest that PRP is correlated with PVD, independent of any effects of vitreous hemorrhage or neovascularization. That the relationship between PRP therapy and the development of PVD is one of cause and effect is consistent with the finding that the incidence and extent of PVD increased with increasing amounts of PRP (Table 2). Previous experimental [22] and clinical [23] studies have suggested that PRP could cause PVD by inducing vitreous liquefaction. However, liquefaction alone is not sufficient to cause PVD [19]; weakening of the vitreoretinal adhesion must also occur.

The extracellular maxtrix at the vitreoretinal interface is purportedly synthesized and maintained by both Müller cells and hyalocytes [20]. It is plausible that PRP injures or alters these cells. The resultant weakening of vitreoretinal adhesion could contribute to the observed development of PVD after PRP. Early studies [18] with xenon arc treatment noted condensation of vitreous collagen fibrils. At the posterior vitreous cortex, laser photocoagulation induces shrinkage and contraction of the collagen fibrils [3, 10] and proliferation of hyalocytes [12, 13]. There is also an influx of serum proteins and enzymes into the vitreous that arise from the photocoagulated choroid and choriocapillaris [14]. All of these phenomena may contribute to liquefaction of the vitreous gel and dehiscence at the vitreoretinal interface, which are necessary for the development of PVD.

It must be emphasized that the population in this study was small and that further study is needed using the same or better vitreous examination techniques. Should subsequent investigations confirm these hypotheses, it may be useful to design laser or other treatments for diabetic patients, with the goal of liquefying the vitreous gel and weakening vitreoretinal adhesion. The prophylactic induction of PVD before the onset of severe neovascularization may be one method to help prevent the serious sequelae of PDR.

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References

1. Benson WE, Spalter HF (1971) Vitreous hemorrhage: a review of experimental and clinical investigations. Surv Ophthalmol 15:297–311
2. Buzney SM, Weiter JJ, Furukawa H, Hirokawa H, Tolentino FI, Trempe CL, Rapp RE (1985) Examination of the vitreous: a comparison of biomicroscopy using the Goldmann and El Bayadi-Kajiura lenses. Ophthalmology 92:1745–1748
3. Campbell CJ, Rittler MC, Spalter HF, Koester CJ (1966) Die Laser-Lichtkoagulation der Netzhaut. Klin Monatsbl Augenheilkd 149:636–648
4. Cunha-Vaz J, Faria de Abreu JR, Campos AJ, Figo GM (1975) Early breakdown of the blood-retinal barrier in diabetes. Br J Ophthalmol 59:649–656
5. Cunha-Vaz JG, Fonseca JR, Abreu JF (1978) Vitreous fluorophotometry and retinal blood flow studies in proliferative retinopathy. Graefe's Arch Clin Exp Ophthalmol 207:71–76
6. D'Amore PA, Glaser BM, Brunson SK, Fenselau AH (1981) Angiogenic activity from bovine retina: partial purification and characterization. Proc Natl Acad Sci USA 78:3068–3072
7. Davis MD (1965) Vitreous contraction in proliferative diabetic retinopathy. Arch Ophthalmol 74:741–751
8. Diabetic Retinopathy Study Research Group (1976) Preliminary report on effects of photocoagulation therapy. Am J Ophthalmol 81:383–396
9. Faulborn J, Bowald S (1985) Microproliferations in proliferative diabetic retinopathy and their relationship to the vitreous: corresponding light and electron microscopic studies. Graefe's Arch Clin Exp Ophthalmol 223:130–138
10. Francois J, Hanssens M (1966) La photocoagulation retinienne au laser. In: Travaux d'ophtalmologie moderne au Dr. Jacques Mawas à l'occasion de son jubilé. Masson, Paris, p 147
11. Glaser BM, Campochiaro PA, Davis JL Jr, Sato M (1985) Retinal pigment epithelial cells release an inhibitor of neovascularization. Arch Ophthalmol 103:1870–1875
12. Gloor BP (1969) Cellular proliferation on the vitreous surface after photocoagulation. Graefe's Arch Clin Exp Ophthalmol 178:99–113
13. Gloor BP (1969) Mitotic activity in the cortical vitreous cells (hyalocytes) after photocoagulation. Invest Ophthalmol 8:633–646
14. Hoffman K, Wurster U (1981) Effects of experimental laser irradiation of the retina on the composition of the vitreous. Dev Ophthalmol 3:146–159
15. Jalkh A, Takahashi M, Topilow HW, Trempe CL, McMeel JW (1982) Prognostic value of vitreous findings in diabetic retinopathy. Arch Ophthalmol 100:432–434
16. Kohner EM, Shilling JS, Hamilton AM (1976) The role of avascular retina in new vessel formation. Metab Ophthalmol 1:15–23
17. Lee PF, McMeel JW, Schepens CL, Field RA (1966) A new classification of diabetic retinopathy. Am J Ophthalmol 62:207–219
18. Okun E, Collins EM (1962) Histopathology of experimental photocoagulation in the dog eye. I. Graded lesions, vitreous effects and complications. Am J Ophthalmol 54:3–16
19. Sebag J (1987) Ageing of the vitreous. Eye 1:254–262
20. Sebag J (1987) Structure, function, and age-related changes of the human vitreous. In: Schepens CL, Neetens A (eds) The vitreous and vitreoretinal interface. Springer, New York Berlin Heidelberg, pp 37–57
21. Sebag J, McMeel JW (1986) Diabetic retinopathy: pathogenesis and the role of retina-derived growth factor in angiogenesis. Surv Ophthalmol 30:377–384
22. Tagawa H, Hirokawa H, Takahashi M, Kanazawa T (1984) Biochemical studies on the mechanism of vitreous liquefaction and detachment: 1. Hyaluronic acid and soluble protein of the vitreous body in rabbit after xenon photocoagulation. Acta Soc Ophthalmol Jpn 88:523–531
23. Tagawa H, McMeel JW, Furukawa H, Quiroz H, Murakami K, Takahashi M, Trempe CL (1986) Role of the vitreous in diabetic retinopathy. I. Vitreous changes in diabetic retinopathy and in physiologic aging. Ophthalmology 93:596–601
24. Tagawa H, McMeel JW, Trempe CL (1986) Role of the vitreous in diabetic retinopathy. II. Active and inactive vitreous changes. Ophthalmology 93:1188–1192
25. Takahashi M, Trempe CL, Schepens CL (1980) Biomicroscopic evaluation and photography of posterior vitreous detachment. Arch Ophthalmol 98:665–668
26. Takahashi M, Trempe CL, Maguire K, McMeel JW (1981) Vitreoretinal relationship in diabetic retinopathy: a biomicroscopic evaluation. Arch Ophthalmol 99:241–245
27. Weiter JJ, Zuckerman R (1980) The influence of the photoreceptor-RPE complex on the inner retina: an explanation for the beneficial effects of photocoagulation. Ophthalmology 87:1133–1139

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