

A proposed new classification for diabetic retinopathy: The concept of primary and secondary vitreopathy

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Background: Many eyes with proliferative diabetic retinopathy (PDR) require vitreous surgery despite complete regression of new vessels with pan retinal laser photocoagulation (PRP). Changes in the vitreous caused by diabetes mellitus and diabetic retinopathy may continue to progress independent of laser regressed status of retinopathy. Diabetic vitreopathy can be an independent manifestation of the disease process.

Aim: To examine this concept by studying the long-term behavior of the vitreous in cases of PDR regressed with PRP.

Materials and Methods: Seventy-four eyes with pure PDR (without clinically evident vitreous traction) showing fundus fluorescein angiography (FFA) proven regression of new vessels following PRP were retrospectively studied out of a total of 1380 eyes photocoagulated between March 2001 and September 2006 for PDR of varying severity. Follow-up was available from one to four years.

Results: Twenty-three percent of eyes showing FFA-proven regression of new vessels with laser required to undergo surgery for indications produced by vitreous traction such as recurrent vitreous hemorrhage, tractional retinal detachment, secondary rhegmatogenous retinal detachment and tractional macular edema within one to four years.

Conclusion: Vitreous changes continued to progress despite regression of PDR in many diabetics. We identify this as "clinical diabetic vitreopathy" and propose an expanded classification for diabetic retinopathy to signify these changes and to redefine the indications for surgery.

Key words: Classification of diabetic retinopathy, intermediate diabetic vitreopathy, primary diabetic vitreopathy, surgical diabetic vitreopathy

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Laser photocoagulation has changed the long-term outcome of proliferative diabetic retinopathy (PDR) and clinically significant macular edema (CSME).^{1,2} About 60 to 75% of PDR cases show complete regression of new vessels with pan retinal laser photocoagulation (PRP).^{1,3} Successfully regressed PDR cases may require to undergo vitreoretinal surgery for different indications during follow up period. This is because of progressive vitreous contraction.^{4,6} The pan metabolic disease of diabetes mellitus (DM) induces changes in vitreous tissue by non-enzymatic glycation of proteins, resembling age-related vitreous degeneration occurring at a much younger age.⁷⁻¹⁰ Proliferative diabetic retinopathy further alters the vitreous by inclusion of vasogenic cells and fibrous tissue.¹¹⁻¹⁴ It is possible that the changes in vitreous due to DM which are independent of retinopathy and the changes in vitreous induced by PDR build indications for vitreoretinal surgery even in laser-treated PDR cases by vitreous contraction such as tractional retinal detachment (TRD), tractional macular edema, secondary

rhegmatogenous retinal detachment and recurrent vitreous hemorrhages.^{4,15-18} The existing classifications of diabetic retinopathy including the modified Airle house classification¹⁹⁻²² do not represent "diabetic vitreopathy" as a clinically identifiable division of the whole pathological complex. This study reviewed a large number of cases and proposed an expanded classification to identify diabetic vitreopathy as a separate class, relatively independent of laser treatment and status of retinopathy. Recently anti vascular endothelial growth factor (anti VEGF) drugs have been used intravitreally to treat difficult PDR cases.²³⁻²⁶ The proposed classification also identifies the indications for use of these drugs based on our concept of diabetic vitreopathy.

Materials and Methods

A total of 1380 eyes were treated with PRP for the indication of PDR from March 2001 to September 2006. The modified Airle house classification was followed. Cases included PDR of varying severity such as flat new vessels, with raised new vessels, subhyaloid hemorrhage, vitreous hemorrhage, TRD and macular edema with and without vitreous traction. Thus in some of these cases the clinical evidence of vitreous contraction²⁷ was already present before laser treatment was applied. In order to study the course of changes in the vitreous tissue over long term, we selected 100 eyes photocoagulated for pure PDR without clinically evident vitreous traction (as defined below).

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Out of these 100 eyes 74 eyes showing complete regression of new blood vessels following PRP were studied over a follow-up period of one to four years.

Criteria for pure PDR (without clinically evident vitreous traction): selection (1 to 5) and follow-up (6 to 7).

1. Proliferative diabetic retinopathy with flat new vessels on the disc (NVD) and /or flat new vessels elsewhere (NVE).^{27,28}
2. Neither hemorrhage in the vitreous nor subhyaloid hemorrhage.
3. No tractional edema of macula.
4. No previous ocular surgery.
5. Absence of systemic hypertension and renal disease.
6. Fundus fluorescein angiography (FFA) proven regression of new vessels after PRP and no recurrence of new vessels during a follow-up of at least one year.
7. Presence of other signs of involution in addition to regression of new vessels such as decrease in venous dilatation, disc pallor, disappearance of retinal hemorrhages.²⁹

Careful history was obtained regarding duration of diabetes, type of diabetes and any other systemic illness (hypertension, renal failure) contributing to retinopathy, concurrent ocular disease and any previous ocular surgery. Cases with such concomitant pathology were not included in the study [Table 1].

Detailed ocular examination including indirect ophthalmoscopy, slit-lamp biomicroscopy, macular examination with three mirror contact lens / 90 D lens and FFA was done. Optical coherence tomography (OCT) was done in 32 eyes with CSME out of 57 eyes (2004 onwards) to rule out vitreous traction. Eyes with any evidence of vitreous traction before PRP were not included in the study.

Pan retinal laser photocoagulation with or without focal /grid macular photocoagulation was done in all the 100 eyes. Green 532 and red 810 diode laser delivered through slit-lamp, were used. Diode laser was preferentially used for macular

photocoagulation in the presence of lenticular opacities.³⁰ A mild grey whitening of retina was the end point of treatment with spot size 200 to 300 μ and exposure duration of 0.1 to 0.25 secs, with power level adjusted to produce the desired reaction. Number of burns varied from 2300 to 3700. The PRP was completed in three to four sittings at intervals of four to seven days each; Mainster 165 panfundoscopic lens was used.

Follow-up was available in terms of visual acuity and ocular examination at the first week in all cases. The FFA was done at six weeks (18 cases), eight weeks (64 cases) and 11 weeks (18 cases).

Results

Seventy-four out of 100 eyes responded by way of complete regression of new vessels with laser photocoagulation [Table 2]. Twenty-six eyes required further PRP or other adjunctive treatment. Out of 57 eyes with macular edema visual improvement of two lines or more was observed in 34 eyes, stabilization of visual acuity in 11 eyes and drop of visual acuity by one line or more in 12 eyes. Sixteen out of these 74 eyes required to undergo vitreo retinal surgery within a period of one to four years after complete regression of new vessels following laser photocoagulation [Table 3]. Other signs of regression of PDR such as disc pallor, ghost vessels and reduced venous dilatation were present in only 39 out of 74 cases.

Incidence of PDR was significantly high in Type I DM (P 0.001) and was observed to increase with duration of DM (P 0.001) [Table 1]. Incidence of PDR with and without CSME was significantly high in the age group 41 to 55 years (P 0.05) and also regression of PDR with PRP (P 0.001) [Table 2]. Indications for vitreo retinal surgery were significantly higher in Type I DM (P 0.01), irrespective of age and duration of DM [Table 3].

Discussion

Diabetes induces pathology throughout the body and also in the vitreous via non-enzymatic glycation of proteins.^{7,10} Advanced glycosylation end products (AGEs) have been

Table 1: Age, sex, type and duration of diabetes mellitus in 100 selected cases

Age (Yrs)	Type 1 DM*	Type II DM*	Sex†		Duration of DM‡		
			F	M	Upto 5 yrs	6-10 yrs	11 yrs or more
25-40	16	05	08	13	04	07	10
41-55	38	14	28	24	04	18	30
56 or more	13	14	08	19	01	07	19
Total	67	33	44	56	9	32	59

* $\chi^2=19.36$ P value 0.001 (significant), † $\chi^2=4.61$ P value 0.10 (not significant), ‡ $\chi^2=27.99$ P value 0.001 (significant); DM-Diabetes mellitus, M- male, F- Female

Table 2: Presentation, laser used and effect of laser (100 cases)

Age (Yrs)	PDR+CSME*	PDR only*	Type of laser†		Regressed‡	
			810 nm	532 nm	810+532	PDR
25-40	07	14	-	21	-	16
41-55	32	20	12	32	8	38
56 or more	18	09	16	02	09	20
Total	57	43	28	55	17	74

* $\chi^2=6.27$ P value 0.05 (significant), † $\chi^2=39.52$ P value 0.001 (significant); PDR - Proliferative diabetic retinopathy, CSME - Clinically significant macular edema

Table 3: Indications for vitreo-retinal surgery in relation to type, duration of diabetes mellitus and interval after successful pan retinal photocoagulation

Age (Yrs)	Type 1*	Type 2*	Duration of DM†			Indications‡				Interval (Yrs)‡			
			Upto 5 yrs	6-10 yrs	11 yrs+	VH	TRD	CRD	TRM	<1	1-2	2-3	3-4
25-40	04	01	01	03	01	03	01	00	01	02	01	02	00
41-55	06	02	00	05	03	04	02	01	01	03	03	01	01
56+	01	02	00	01	02	01	01	00	01	00	00	02	01
Total	11	05	01	09	06	08	04	01	03	05	04	05	02

DM- Diabetes mellitus, VH- Vitreous hemorrhage, TRD-Tractional retinal detachment, CRD-Combined retinal detachment, TRM-Tractional macular edema;

* $\chi^2 = 13.53$ P value 0.01 (significant), † $\chi^2 = 7.89$ P value 0.50 (not significant), ‡Test not applicable.

found to be elevated in the vitreous of diabetics along with aggregation of collagen fibers and alterations in the cortex and hyalocytes.^{8,31} The vitreous in diabetics shows glycosylated collagen and increased amount of other proteins.^{7-9,32} Degenerative vitreous changes occurring in diabetics at a much younger age produce anomalous PVD, which has been said to help formation of new retinal vessels.^{9,33} Structural changes at the vitreoretinal interface promote migration and proliferation of vasogenic cells in the vitreous, consequent contraction can produce vitreous hemorrhage and macular edema.^{12,34}

Advanced glycation end products correlate with glycemic control and these reactive compounds form on DNA, lipids and proteins where they represent pathophysiological modifications that precipitate dysfunction at a cellular and molecular level in diabetics.^{10,34}

Though the term “diabetic vitreopathy” exists in the literature it has not been used to address and identify the pathological complex of diabetic retinopathy in any of the existing classifications of diabetic retinopathy.¹⁹⁻²² We suggest that changes in the vitreous primarily due to diabetes mellitus and occurring independent of diabetic retinopathy can be called “primary diabetic vitreopathy”. The methods currently available for examination of the vitreous *in vivo* including OCT give good information about the vitreo retinal interface but not the vitreous body, therefore such changes in the vitreous may not be easily detected clinically. We may therefore also call ‘primary diabetic vitreopathy’ as ‘subclinical diabetic vitreopathy’.³³

The hallmark of PDR is development of new vessels. The growing vascular endothelium combines with the collagen of the vitreous and gives it a contractile property.^{2,13,14} Simultaneously fibrous tissue developing along the new vessels lines up on the posterior hyaloid, this also imparts contractile property to the vitreous.¹¹ Contraction of the vitreous can pull new retinal vessels to produce a bleeding in the subhyloid space to begin with [Fig. 1]. If the bleeding is forceful or the vitreous largely liquefied this blood can break into the vitreous tissue concurrently or later. It should be noted here that bleeding outside the tissue confines of retina (internal limiting membrane) is produced by vitreous contraction and not proliferative retinopathy *per se* and thus any hemorrhage outside the retinal tissue whether subhyloid or in the vitreous should be considered a sign of vitreopathy and not retinopathy. Bleeding further augments the contractile property of the vitreous by inclusion of vasogenic and fibrogenic elements and such recurrent bleeding may result in the formation of fibrovascular tissue in the vitreous cavity. Ongoing contraction of vitreous can result in TRD [Fig. 2], secondary rhegmatogenous retinal detachment, persistent macular edema,

premacular hemorrhage in addition to recurrent vitreous hemorrhage.^{35,36} We propose to call the changes induced in the vitreous tissue by proliferative retinopathy ‘secondary diabetic vitreopathy’ or ‘clinical diabetic vitreopathy’. These are mainly in the form of an increase in the contractility and detachment of the vitreous. These changes are different from the changes of ‘primary diabetic vitreopathy’.

If total vitreous detachment was present before development of PDR no bleeding or tractional retinal detachment may occur.



Figure 1: Recurrent premacular hemorrhage, regressed proliferative diabetic retinopathy, note ghost vessels, disc pallor, 1.3 years post pan retinal photocoagulation

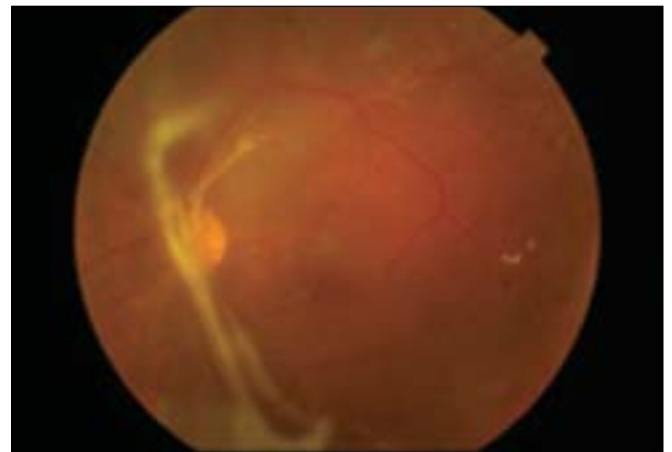


Figure 2: Macular tractional retinal detachment, four years post pan retinal photocoagulation, regressed retinopathy, no intermittent bleeding

Similarly, if there was no separation of vitreous subsequent to development of retinal new vessels the above pathological events may not occur. There have been several attempts in the past for pharmacological vitreolysis so as to abort any complications of retinal neovascularization by pull of vitreous and there is a continuous suggestion in the literature for early vitrectomy in PDR cases with good vision so as to forestall the complications produced by vitreopathy.³⁷⁻³⁹ However, the changes in the vitreous have never been included in any of the classifications of diabetic retinopathy.

Laser ablation of the retina induces regression of new vessels in about two-thirds of cases.¹⁻³ This results in the disappearance of a ready source of bleeding i.e. new vessels. With laser treatment the incidence of non-resolving massive vitreous hemorrhage has drastically reduced. But the other indications for vitreous retinal surgery such as TRD, rhegmatogenous retinal detachment [Fig. 3], tractional macular edema, premacular fibrosis, small recurrent vitreous hemorrhages, retinal wrinkling, macular heterotopia and dense premacular hemorrhage have persisted.^{4-6,15-18} These are all produced by vitreopathy, vitreous traction and not by PDR alone.

In our series, out of 74 eyes showing complete regression

of new vessels with PRP, 16 eyes (23%) required to undergo vitreous surgery for the indications of recurrent vitreous hemorrhage (eight), tractional retinal detachment (four)

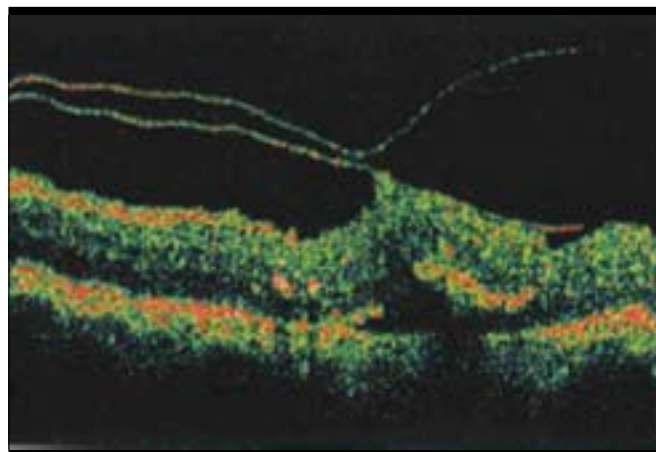


Figure 4B: Optical coherence tomography of 4A showing vitreous traction

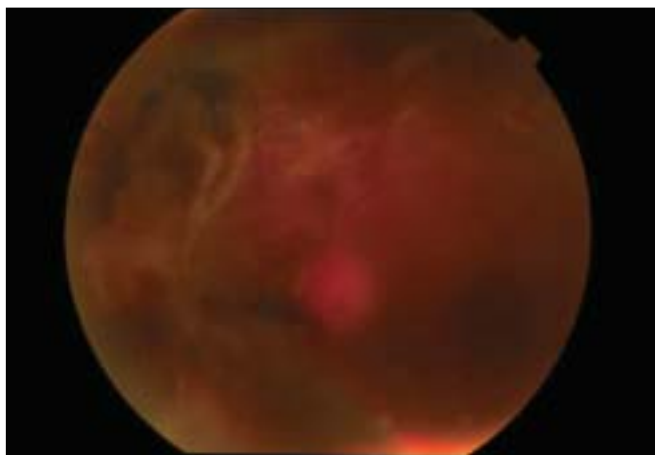


Figure 3: Combined retinal detachment, 1.8 years after successful pan retinal photocoagulation

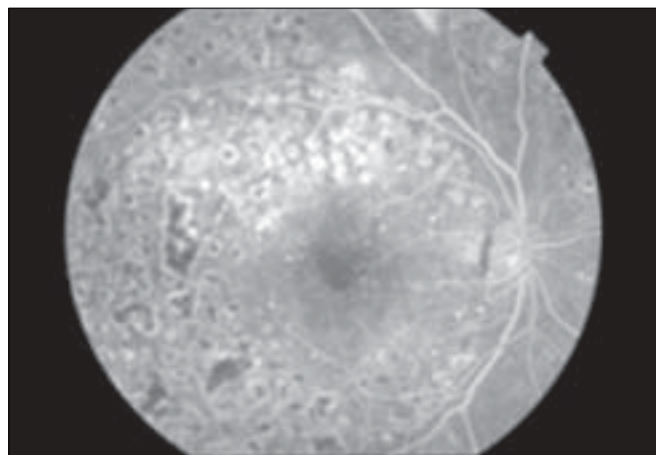


Figure 4C: Fundus fluorescein angiography of 4A, no new vessels on disc, no new vessels elsewhere and no leak

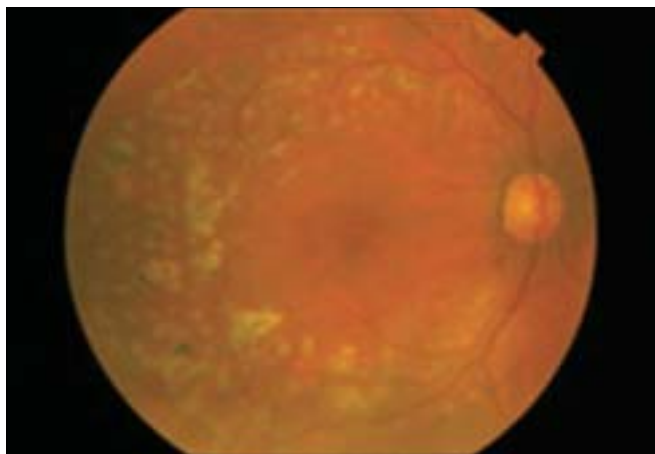


Figure 4A: Two-year-old grid with pan retinal photocoagulation, regressed retinopathy, showing fall of visual acuity due to macular edema



Figure 5: Tractional retinal detachment, retinal wrinkling three years after successful pan retinal photocoagulation

secondary rhegmatogenous retinal detachment(one) and tractional macular edema (three cases) [Fig.4 A,B,C]. In other words 23% of cases showed a continued contraction of vitreous strong enough to produce the indications for surgery despite successful regression of new vessels. We invited data from leading retina centers in the country on incidence of vitreous surgery in cases of PDR fully regressed with PRP, over a period of one to four years. The reported incidence ranged from 18 to 32%. It is logical to say that in these cases the changes of primary /secondary diabetic vitreopathy were relatively independent of the effect of laser treatment and the regressed status of PDR. In the remaining 77% cases there are several factors which explain the absence of complications produced by diabetic vitreopathy. Regression of new vessels is withdrawal of a ready source of bleeding, multiple chorioretinal adhesions produced by laser protect against TRD and rhegmatogenous retinal detachment. Laser treatment in cases with CSME helps resolution of edema, it is effective in tractional macular edema also if the vitreous traction is not very strong. In addition to the above, PRP induces posterior vitreous detachment in 50% cases and in the large majority this is eventless. A small percentage of these cases may show vitreous bleeding or even TRD during completion of PRP if it is too aggressive and spaced closely.⁴⁰ We therefore understand that in the large majority of cases (77% in our series) a balance is established between the beneficial effect of laser on retina and the damaging effect of diabetic vitreopathy. In the remaining cases (23% in our series) this balance might not be established and ongoing vitreous contraction might have produced indications for vitreo retinal surgery. Another aspect of the effect of laser photocoagulation is that though the new vessels disappear the fibrous tissue does not and a slow, late cicatrization of fibrous tissue can produce indications like retinal wrinkling, macular heterotropia⁴¹ and shallow TRD; we had one such case in our series with retinal wrinkling and TRD occurring in regressed retinopathy after a quiet period of three years [Fig. 5].

We suggest diabetic vitreopathy as a separate subdivision in the existing classification of diabetic retinopathy, identifying the changes induced by diabetes mellitus as “primary diabetic vitreopathy” and the changes induced by PDR as “secondary diabetic vitreopathy”. It is the changes of secondary diabetic vitreopathy which can be clinically observed and which produce the indications for vitreo retinal surgery, these can be called “diabetic vitreopathy” as such or “clinical diabetic vitreopathy”. We further observe that certain cases of clinical diabetic vitreopathy might not be operable because of extensive neovascularization both in the anterior and posterior segment or many complex fibrovascular membranes in the vitreous. In other words we can have cases which are operable and may benefit by vitreous surgery i.e. ‘surgical vitreopathy’ and cases which are inoperable or may not benefit by vitreous surgery i.e. ‘non surgical vitreopathy’.

Recently, intravitreal drugs have been used to alter the course of PDR. Two main groups of drugs have been used. First is purified ovine hyaluronidase (Vitrase, ISTA pharmaceuticals) which produces vitreous liquefaction. The second group are anti-VEGF drugs, which reduce neovascularization, contraction of fibrovascular proliferations when PRP is applied and bleeding during surgery. Avastin (Genetech Pharmaceuticals), the commonest drug, has been used as a preoperative adjunct for PDR, TRD with severe PDR, for iris rubeosis, florid disc

neovascularization and for treatment of PDR complicated by vitreous hemorrhage.²³⁻²⁶

This would mean that anti-VEGF drugs can be used in cases which are either inoperable because of extensive neovascularization, massive vitreous hemorrhage or are risky to operate due to the possibility of intraoperative bleeding and other complications. Use of these drugs may render such cases suitable for surgery. In order to identify such cases in a logical manner we suggest a separate class in between surgical and non-surgical vitreopathy as “intermediate vitreopathy”. The cases put in this class can shift to the surgical vitreopathy group if response to drug is adequate and to the non-surgical vitreopathy group if the drug treatment does not make the case operable.

We suggest the following revised classification for diabetic retinopathy.

The term “Diabetic Retinopathy” may be replaced by “Diabetic Retino-vitreopathy” and may be classified as below.

Dubey’s classification of diabetic retino-vitreopathy

1. Non-proliferative diabetic retinopathy (mild/moderate/severe/very severe)
2. Proliferative diabetic retinopathy
3. Diabetic maculopathy (focal, diffuse, ischemic, mixed)
4. Clinical diabetic vitreopathy
 - i) Surgical vitreopathy
 - ii) Intermediate vitreopathy
 - iii) Non-surgical vitreopathy

Surgical vitreopathy

- i) Posterior pole TRD⁵
- ii) Superior half TRD¹⁶
- iii) Tractional macular edema without macular ischemia¹⁵
- iv) Premacular fibrosis²⁸
- v) Recurrent vitreous hemorrhages in laser regressed PDR^{4,17}
- vi) Secondary rhegmatogenous retinal detachment²⁷⁻²⁸
- vii) Optic disc traction²⁷⁻²⁸
- viii) Macular heterotropia⁴¹
- ix) Retinal wrinkling⁴¹
- x) Dense premacular hemorrhage³⁵

Intermediate vitreopathy

- i) Florid neovascularization with /without any of the above indications²⁶
- ii) Anterior segment neovascularization²⁴
- iii) Neovascularization non-responsive to laser with/without any of the above indications²⁴⁻²⁶
- iv) Large non-resolving vitreous bleeding in laser-treated or untreated PDR²⁶

Non-surgical vitreopathy

- i) Inferior peripheral TRD¹⁶
- ii) Recurrent vitreous hemorrhages in active PDR^{28,36}
- iii) Tractional macular edema with ischemia^{15,27}

This classification represents all stages and manifestations of diabetic retinopathy including changes in the vitreous. The classification identifies surgical indications and places different

manifestations in accordance with the pathology and indicated treatment. For example, tractional diabetic macular edema is classified as surgical vitreopathy as it is the vitreous traction which is the cause and surgery is the treatment.

The classification incorporates the indications for using recent intravitreal anti-VEGF drugs also.

The study sets the direction for further research and investigations on vitreous changes using modern tools such as ultrasound and OCT in diabetics before and after development of diabetic retinopathy and also long-term prospective observations on the retina and vitreous on a larger sample of PDR cases after PRP. Long-term observations following administration of anti-VEGF drugs are indicated.

Conclusion

Diabetic retino vitreopathy is the suggested new nomenclature for diabetic retinopathy. Changes in the vitreous induced by diabetes mellitus are identified as primary diabetic vitreopathy/subclinical diabetic vitreopathy and changes induced by proliferative retinopathy as secondary diabetic vitreopathy/clinical diabetic vitreopathy. Any indications for vitreous surgery in PDR are produced by vitreopathy and not retinopathy *per se*.

In about two-thirds of PDR cases vitreopathy can be kept under control with adequate PRP, the remaining one-third cases may require surgery due to vitreopathy. A new classification is proposed taking into consideration the element of diabetic vitreopathy as well as the clinical use of intravitreal anti-VEGF drugs.

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