Evaluation of the Posterior Hyaloid Changes Following Intravitreal Injection of Ranibizumab for Diabetic Macular Edema

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Purpose
The aim of this work was to evaluate the posterior hyaloid changes and the effect on the vitreomacular relationship following intravitreal injection of ranibizumab (lucentis) for DME in diabetic patients attending the outpatient clinic of the Ophthalmology Department in Alexandria Main University Hospital.

Patients and methods
The study included 40 eyes. All of them received a baseline injection of 0.5 mg of intravitreal ranibizumab under sterile conditions. The injection was performed under topical anesthesia, with or without sedation. Further injections were administered Pro Re Nata (PRN 'as required') as decided in each subsequent follow-up visit if central retinal thickness remained 300 μm or greater or if there was a decrease in best-corrected visual acuity due to DME progression, confirmed with clinical evaluation and/or optical coherence tomography or other anatomic and clinical assessments.

Results
There were 12 male (54.2%) and 10 female patients (45.5%) between 45 and 71 years of age, with a mean value of 63.2 ± 12.6. There were five patients (22.7%) with type I and 17 patients (77.3%) with type II DM. The duration of DM was less than 10 years in six patients (27.3%) and more than 10 years in 16 patients (72.7%); it ranged between 9.5 and 20 years, with a mean value of 15.11 ± 7.98 years. HbA1c ranged from 7.11 to 8.25, with a mean value of 7.72 ± 0.892, and baseline visual acuity (TTDRS) ranged from 7.11 to 8.25, with a mean value of 53.13 ± 12.22. Baseline central macular thickness ranged from 301.0 to 525.0, with a mean value of 413.0 ± 107.0. No vitreous separation (category 1) was observed in 19 cases (47.5%), partial vitreomacular separation (VMS) (category 2) was observed in 12 cases (30%), vitreofoveal attachment with no traction (category 3) in seven cases (17.5%), and finally vitreofoveal attachment with traction (dome-shaped profile) (category 4) was observed in two cases (5%). No changes in vitreomacular relationship was seen in 16 cases (40%), partial VMS was seen in six cases (15%), vitreofoveal attachment with no traction was seen in eight cases (20%), vitreofoveal attachment with traction (dome-shaped profile) in three cases (7.5%), and complete VMS was seen in seven cases (17.5%). There was a statistically significant difference with regard to number of changes in VMR, partial VMS, vitreofoveal attachment with no traction, and vitreofoveal attachment with traction (dome-shaped profile). There was a statistically significant difference with regard to partial VMS, vitreofoveal attachment with no traction, and vitreofoveal attachment with traction (dome-shaped profile). There was a statistically significant relation between the number of injections and the outcome; the higher the number of injections, the better is the outcome.

Keywords:
antiVEGF, DME, intravitreal, posterior hyaloid, ranibizumab

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Introduction

An estimated 346 million people were affected by diabetes worldwide in 2011, and the number of people with the disease is expected to double from 2005 to 2030 [1].

Diabetic retinopathy (DR) is characterized by the development of microvascular leakage and focal areas of retinal ischemia in nonproliferative diabetic retinopathy (NPDR), or by revascularization originating from the disc and peripheral retina in response to widespread retinal ischemia in proliferative diabetic retinopathy (PDR). Upregulation of vascular endothelial growth factor

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(VEGF) mRNA and marked immunohistochemical microvascular staining for the factor have been demonstrated in the retinas of patients with PDR [2]. DR is the leading cause of loss of vision in adults of working age [3], and diabetic macular edema (DME) is the most frequent cause of vision loss related to diabetes, especially in patients with a long duration of disease.

Several studies have demonstrated significantly elevated levels of VEGF in ocular fluids from patients with active diabetic proliferative disease compared with patients with inactive proliferative disease, after extensive laser surgery, or those with NPDR. None of the other known angiogenesis factors, except insulin-like growth factor-1, show such a strong correlation with ischemia-related ocular angiogenesis in humans [4–6].

More localized retinal expression of VEGF may only lead to increased microvascular permeability, as recent work suggests that VEGF is also upregulated in NPDR and other causes of retinal edema [7].

Argon laser photocoagulation has been the mainstay of treatment for macular edema since the publication of the results of the Early Treatment Diabetic Retinopathy Study. Over the last few years, intravitreal corticosteroids and intravitreal anti-VEGF agents have also entered common clinical use, either alone or in combination with focal/grid laser, for the management of DME, and several recent randomized clinical trials have shown improved effectiveness compared with focal/grid laser [8,9].

However, there have been patients with diffuse DME refractory to such treatment modalities. In cases of intractable diffuse DME that persists or recurs after laser photocoagulation or intravitreal triamcinolone injection, limited treatment benefits are expected. This is because of the structural damage caused by chronic macula edema and the underlying DR.

The vitreous and vitreoretinal junction have been identified as being modulators of DME [10], although their precise role in the pathogenesis of diabetic maculopathy is widely debated [11]. Encouraged by reports showing that diabetic patients with posterior vitreous detachment (PVD) are less likely to develop DME [12] and that resorption may occur after spontaneous PVD [13], vitrectomy with the removal of the posterior hyaloid has been considered to be a therapeutic option in diffuse and cystoid edema, which often persists despite multiple laser treatments [14]. Successful vitrectomy has been reported not only in selected patients with DME associated with visible posterior hyaloid traction but also reported in eyes when macular traction was stated to be absent [14,15].

The aim of this work was to evaluate the posterior hyaloid changes and the effect on the vitreomacular relationship (VMR) following intravitreal injection of ranibizumab (lucentis) for DME in diabetic patients attending the outpatient clinic of the Ophthalmology Department in Alexandria Main University Hospital.

Patients and methods

Patient eligibility

Inclusion criteria

(1) Having type 1 or type 2 diabetes and DME with a visual acuity between 20/40 and 20/160 (approximate Snellen equivalent), central retinal thickness of 300 μm or greater, and decreased vision attributed to foveal thickening from DME that was not explained by any other cause.
(2) Absent epiretinal hyper-reflectivity on optical coherence tomography (OCT) (i.e. no epimacular traction).
(3) Providing informed consent.

Exclusion criteria

(1) A history of laser or surgical intervention for DR.
(2) Any recent evident history of ocular trauma.
(3) PVD (defined by the absence of the posterior hyaloid face on baseline OCT and/or the presence of Weiss ring).
(4) Having epimacular membrane (i.e. epiretinal traction documented with OCT).
(5) Fluorescein angiography evidence of macular ischemia. Macular ischemia was graded from 0 to 4. Four quadrants were marked out within a 0.5 disc diameter marker centered on the fovea. Macular ischemia was defined as more than two consecutive quadrants of disrupted or enlarged foveal avascular zone.

Preoperative examination

The patients included in this study were subjected to the following:

(1) Complete history taking

(a) Age.
(b) Medical history [disease duration, type of diabetes mellitus (DM), and control status].
(c) Ophthalmological history (glaucoma and ophthalmic surgeries).
(d) History of trauma (duration).
(e) Drug history (systemic or topical).
(f) Family history.

(2) Complete ophthalmological examination
Refraction and best-corrected visual acuity.
Slit-lamp biomicroscopy of the anterior segment.
Intraocular pressure measurement using the Goldmann applanation tonometer.
Posterior segment evaluation using fundus biomicroscopy (the presence or absence of the Weiss ring was documented).

(3) Fluorescein angiography (using 10% concentration of fluorescein):

Standby antiemetic, antihistaminic, and dexamethasone ampules should always be available during the angiography for the first aid management of any mild, moderate, or severe adverse reactions.

OCT was used to assess vitreomacular interface changes and macular mapping. It is a medical diagnostic imaging technology that can perform micron resolution cross-sectional or tomographic imaging in biological tissue. The technique of OCT is analogous to ultrasound B-mode or radar, except that light is used rather than acoustic or radio waves. OCT is especially suited for diagnostic applications in ophthalmology because of the ease of the optical access to anterior and posterior segments of the eye [16].

Ranibizumab (lucentis) injection

The study included 40 eyes; all of them received a baseline injection of 0.5 mg of intravitreal ranibizumab under sterile conditions. The injection was performed under topical anesthesia, with or without sedation. Further injections were administered Pro Re Nata (PRN 'as required') as decided in each subsequent follow-up visit if central retinal thickness remained 300 μm or greater or if there was a decrease in best-corrected visual acuity due to DME progression, confirmed by means of clinical evaluation and/or OCT or other anatomic and clinical assessments.

Optical coherent tomography

The OCT (Cirrus HD-OCT model 4000; Carl Zeiss Ophthalmic Systems-Humphrey Division, Dublin, California, USA) was used in the assessment of central macular thickness (CMT) and VMR at baseline and then monthly until 6 months of follow-up. The CMT was computed automatically using a built-in OCT retinal mapping software. Caliper measurement was used for cases in which automatic computation was shown to be unreliable. For each eye, images were scrutinized for evidence of changes in the vitreoretinal interface. The evolution of PVD was grouped (graded) into six categories on OCT images.

(1) No vitreomacular separation (VMS).
(2) Partial VMS: separation of the vitreous from the nasal or the temporal retina.
(3) Perifoveal VMS
(a) Without traction – defined as perifoveal separation of the vitreous with no dome-shaped configuration of the retina.
(b) With traction – defined as perifoveal separation of the vitreous with dome-shaped configuration of foveal depression.
(4) VMS – defined as detecting the posterior hyaloid face without any macular attachments on OCT.
(5) PVD – defined as the absence of the posterior hyaloid face on OCT and the presence of Weiss ring on biomicroscopy.

OCT evidence of epiretinal membrane characterized by a thick hyper-reflective band at the vitreoretinal was also documented. All patients were assessed at every visit with refraction, clinical examination, and OCT. The final visual outcomes defined as mean ETDRS letters gained or lost at the end of 6 months and mean changes in macular thickness (final CMT-initial CMT) were compared in the five groups.

Results

Table 1 shows demographic data of the studied groups. The number of patients was 22 (eyes 40). There were four unilateral cases (18.2%) and 18 bilateral cases (81.8%).

There were 12 male (54.2%) and 10 female patients (45.5%) between 45 and 71 years of age, with a mean value of 63.2 ± 12.6 years.

There were five patients (22.7%) with type I and 17 patients (77.3%) with type II DM. The duration of DM was less than 10 years in six cases (27.3%) and more than 10 years in 16 cases (72.7%); it ranged from 9.5 to 20, with a mean value of 15.11 ± 7.98.

HbA1c ranged from 7.11 to 8.25, with a mean value of 7.72 ± 0.892. Baseline visual acuity (TTDRS) ranged from 7.11 to 8.25 with a mean value of 53.13 ± 12.22.

Baseline CMT ranged from 301.0 to 525.0, with a mean value of 413.0 ± 107.0.

Table 2 shows baseline patterns of VMR. No vitreous separation (category 1) was observed in 19 cases (47.5%), partial VMS (category 2) was observed in 12 cases (30%), vitreofoveal attachment with no traction (category 3) was seen in seven cases (17.5%), and finally vitreofoveal attachment with traction (dome-shaped profile) (category 4) was observed in two (5%).

Table 1 Demographic data of the studied groups

	Number (%)
Number of patients	22
Number of eyes	40
Unilateral	4 (18.2)
Bilateral	18 (81.8)
Age	
40–50	3 (13.6)
50–60	4 (18.2)
60 or more	15 (68.2)
Range	45–71
Mean	63.2
SD	12.6
Sex	
Male	12 (54.5)
Female	10 (45.5)
Type	
I	5 (22.7)
II	17 (77.3)
Duration of DM (years)	
<10	6 (27.3)
>10	16 (72.7)
Range	9.5–20.0
Mean	15.11
SD	7.98
HbA1c	
Range	7.11–8.25
Mean	7.72
SD	0.892
Baseline visual acuity (ETDRS)	
Range	40.0–68.0
Mean	53.13
SD	12.22
Baseline CMT	
Range	301.0–525.0
Mean	413.0
SD	107.0

CMT, central macular thickness; DM, diabetes mellitus.

Table 2

Vitreous changes	Number (%)
No vitreous separation (category 1)	19 (47.5)
Partial VMS (category 2)	12 (30.0)
Vitreofoveal attachment with no traction (category 3)	7 (17.5)
Vitreo-foveal attachment with traction (dome shaped profile) (category 4)	2 (5.0)

VMS, vitreomacular separation. [a]No vitreous separation. [b]Partial vitreous separation. [c]Perifoveal vitreous detachment with no traction. [d]Perifoveal vitreous detachment with traction.

Tomographic appearance of different stages of vitreomacular relationship

Table 3 shows acquired changes in VMR during the 6-month follow-up. No changes in VMR was observed in 16 cases (40%), partial VMS was observed in six cases (15%), vitreofoveal attachment with no traction was seen in eight cases (20%), vitreofoveal attachment with traction (dome-shaped profile) was seen in three cases (7.5%), and complete VMS was observed in seven cases (17.5%).

A case of category 1 VMR (no VMS) with diffuse DME received three subsequent intravitreal ranibizumab injections and resulted in a remarkable improvement in CMT without change in VMR.

A case of category 4 VMR (perifoveal vitreous detachment with traction) and diffuse DME received five subsequent intravitreal ranibizumab injections and resulted in a remarkable improvement in CMT with complete VMS.

A case of category 1 VMR (no VMS) and focal DME received one intravitreal ranibizumab injection and resulted in an evident improvement in CMT with complete VMS.

A case of category 4 VMR (perifoveal vitreous detachment with traction) and multifocal DME received three intravitreal ranibizumab injections and resulted in an evident improvement in CMT with complete VMS.

A case of category 3 VMR (perifoveal vitreous detachment with no traction) and multifocal DME received three subsequent intravitreal ranibizumab injections and resulted in poor outcome and worsening of the CMT with evolution of the VMR to perifoveal vitreous detachment with traction.

Table 3

Vitreous changes	Number (%)
No changes in VMR	16 (40.0)
Partial VMS	6 (15.0)
Vitreofoveal attachment with no traction	8 (20.0)
Vitreofoveal attachment with traction (dome-shaped profile)	3 (7.5)
Complete VMS	7 (17.5)

VMR, vitreomacular relationship; VMS, vitreomacular separation.

Table 4 shows the influence of changes in VMR on visual outcome. There was a statistically significant difference as regards the number of changes in VMR, partial VMS, vitreofoveal attachment with no traction, and vitreofoveal attachment with traction (dome-shaped profile) ($P<0.05$).

Table 5 shows influence of changes in VMR on CMT. There was a statistically significant difference as regards partial VMS, vitreofoveal attachment with no traction, and vitreofoveal attachment with traction (dome-shaped profile) ($P<0.05$).

Table 6 shows the relationship between the number of injection and the outcome.

There was a statistically significant relation between the number of injection and the outcome; the higher the number of injections, the better is the outcome ($P<0.05$) (Figs. 1–11).

Discussion

The study included 40 eyes. All of them received a baseline injection of 0.5 mg of intravitreal ranibizumab under sterile conditions.

The results of this study demonstrate that changes in VMR influence the outcome of treatment with intravitreal ranibizumab for DME.

Uchino *et al.* [17] studied the role of the vitreous in the development and progression of DME. Vitrectomy with or without the peeling of internal limiting membrane has been investigated as a treatment alternative for refractory DME.

Surgical separation of the posterior hyaloid appears to relieve vitreomacular traction in both anteroposterior and tangential dimensions but the visual results are variable. This study shows an evolution of vitreous

Table 4

Acquired vitreous changes at the end of the study	Changes in ETDRS letters	*P* value
No changes in VMR	1.21±0.103	0.0021*
Partial VMS	1.1±0.085	0.001*
Vitreofoveal attachment with no traction	–1.33±0.107	0.003*
Vitreofoveal attachment with traction (dome-shaped profile)	–8.60±1.32	0.001*
Complete VMS	6.82±1.001	

P comparison between all results in relation to complete VMS. VMR, vitreomacular relationship; VMS, vitreomacular separation.
*Statistically significant.

Table 5

Acquired vitreous changes at the end of the study	Changes in CMT	*P* value
No changes in VMR	–86.8±9.12	0.103
Partial VMS	2.3±0.98	0.001*
Vitreofoveal attachment with no traction	7.7±1.02	0.001*
Vitreofoveal attachment with traction (dome-shaped profile)	28.26±2.10	0.001*
Complete VMS	–111.0±10.25	

CMT, central macular thickness; VMR, vitreomacular relationship; VMS, vitreomacular separation. *Statistically significant.

Table 6

Number of injection	Number of eyes	Outcome at end of follow-up [*n* (%)]	Partial	Vitrofoveal attachment with no traction	Vitreofoveal attachment with traction	Complete VMS
		No changes				
1	1	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2	9	5 (55.6)	3 (33.3)	0 (0.0)	1 (11.1)	0 (0.0)
3	13	7 (53.8)	1 (7.7)	1 (7.7)	2 (15.4)	2 (15.4)
4	8	2 (25.0)	1 (12.5)	3 (37.5)	0 (0.0)	2 (25.0)
5	9	1 (11.1)	1 (11.1)	4 (44.4)	0 (0.0)	3 (33.3)
P	0.0136*					

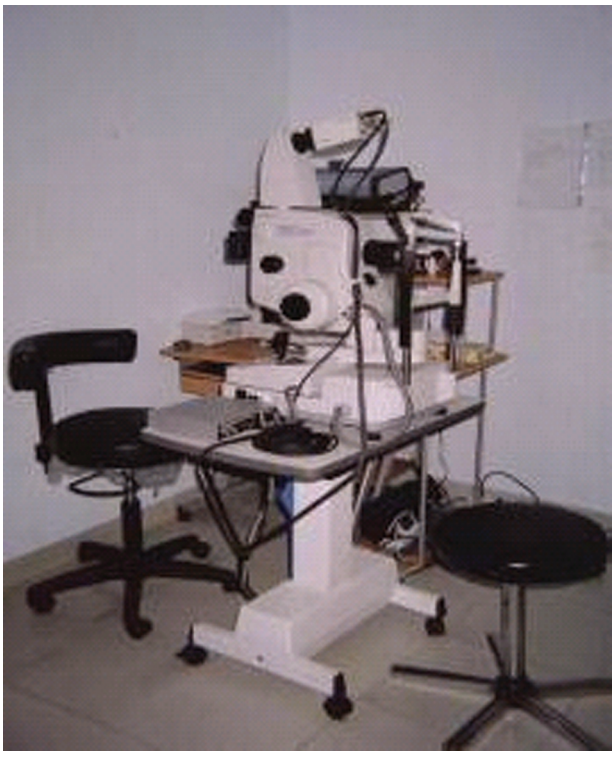
changes after intravitreal ranibizumab. It is possible that the stages evolve from VMS not involving the fovea to perifoveal vitreous detachment and finally to complete VMS. However, it is not necessary for the changes to evolve through all these stages. They only represent different stages of the same process of PVD [18].

The mechanism of action of ranibizumab was previously discussed. This study defines additional effect of intravitreal ranibizumab on the structure of the vitreous and it seems that, in addition to the pharmacological effects on macular edema, intravitreal ranibizumab may induce changes in VMR. The underlying mechanisms of these changes are not clear. It may be that intravitreal ranibizumab accelerates biomechanical changes in the vitreous structure associated with DR and/or normal aging. In addition, the injection procedure may trigger mechanical effects such as vitreous reflux, anterior vitreous incarceration, or induce a local inflammatory reaction. The CMT reduces significantly more when VMS is induced by intravitreal injection of ranibizumab. This anatomical improvement was translated into better visual function. Uchino *et al.* [17]and associates reported the OCT features of the PVD process in normal individuals and showed that PVD starts progressively from the macular periphery towards the fovea before complete separation.

The process of perifoveal separation is exaggerated in DME [18].

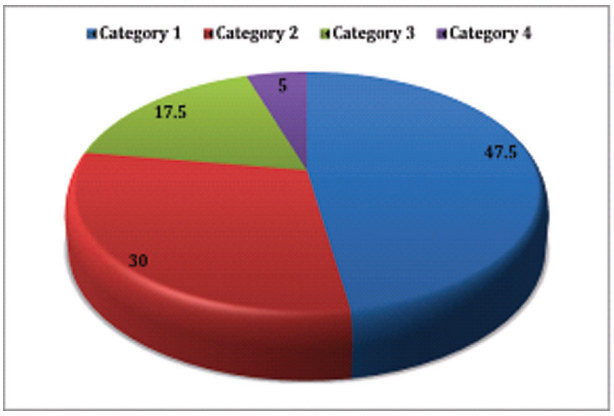
The results of this study indicate that intravitreal injection of ranibizumab may precipitate vitreous separation from the macula and the stage of vitreous separation influences the final CMT and the visual outcome. Patients with perifoveal vitreous detachment with traction had the worst visual prognosis. However, not all patients with perifoveal separation progressed to this configuration. Instead, most developed VMS, and it is surprising that the development of VMS after the stage of macular traction was not followed by visual improvement. Histopathologic evidence of splitting of vitreous cortex is reported in PDR.

Figure 1



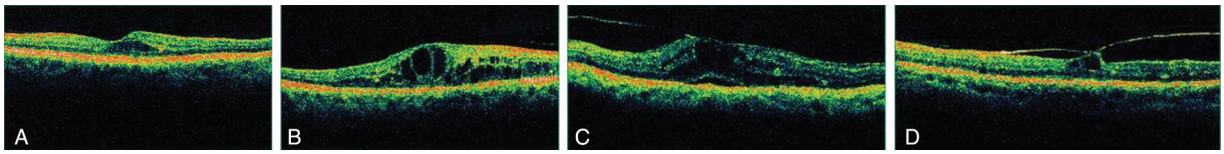
Optical coherence tomography used in the study.

Figure 2



Tomographic appearance of different stages of vitreomacular relationship.

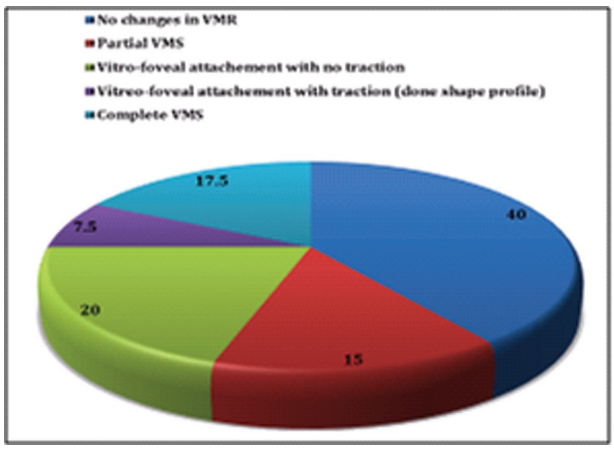
Figure 3



A. No vitreous separation. B. Partial vitreous separation. C. Peri-foveal vitreous detachment with no traction. D. Perifoveal vitreous detachment with traction.

It may be that intravitreal injection of ranibizumab induces vitreoschisis and detaches only the anterior layer of the posterior hyaloids, leaving the posterior leaf attached.

Figure 4

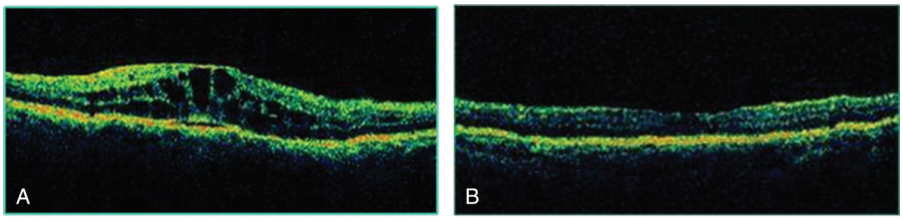


Acquired changes in vitromacular relationship during 6 months follow up.

Moreover, these patients showed persistent angiographic evidence of cystoid macular edema despite developing VMS subsequently, indicating structural damage of the macular vasculature. It is likely that persistent cellular damage prevents significant improvement in VA despite complete VMS and decrease in CMT. Although this study shows that intravitreal ranibizumab perhaps plays a role in visual improvement by promoting vitreous detachment, experience shows that macular edema usually recurs after the period of efficacy has expired whether or not the vitreous is detached. These results are in agreement with those of Schwartz *et al.* [19].

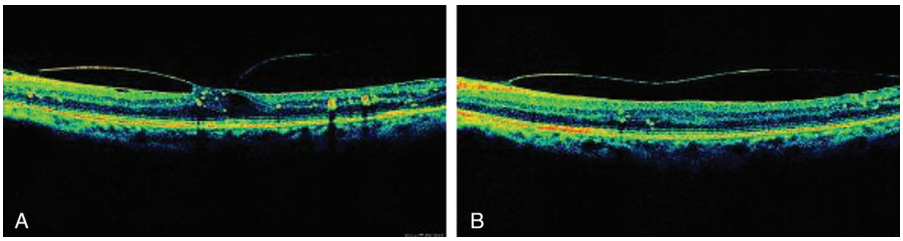
Sivaprasad *et al.* [18] shows an evolution of vitreous changes after intravitreal triamcinolone injection and macular laser. It is possible that the stage evolved from VMS not involving the fovea to perifoveal vitreous detachment and finally to complete VMS.

Figure 5



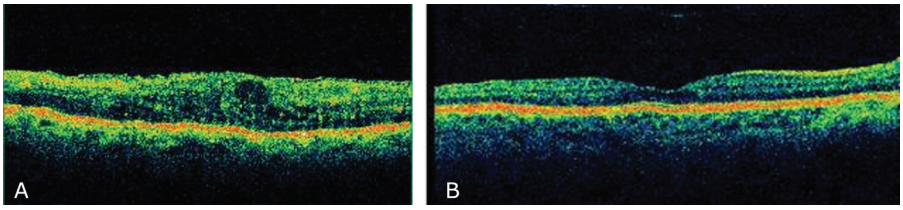
An example of category 1 VMR (no VMS) with diffuse DME, received 3 subsequent intravitreal Ranibizumab injections, resulted in marvellous improvement in CMT without change in VMR.

Figure 6



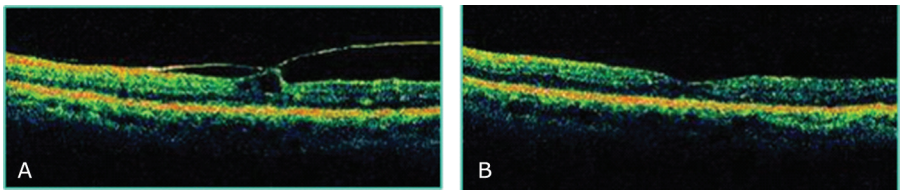
An example of category 4 VMR (perifoveal vitreous detachment with traction) and diffuse DME, received 5 subsequent intravitreal Ranibizumab injections, resulted in marvellous improvement in CMT with complete VMS.

Figure 7



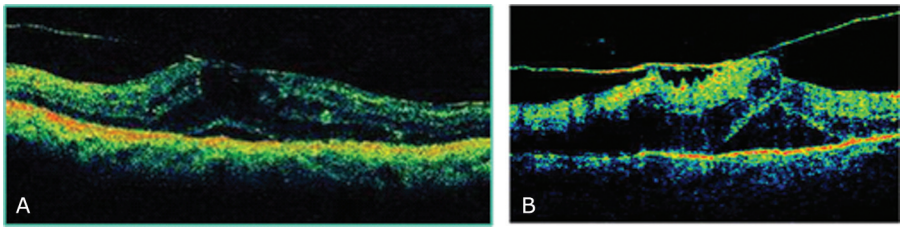
An example of category 1 VMR (no VMS) and focal DME, received 1 intravitreal Ranibizumab injection, resulted in evident improvement in CMT with complete VMS.

Figure 8



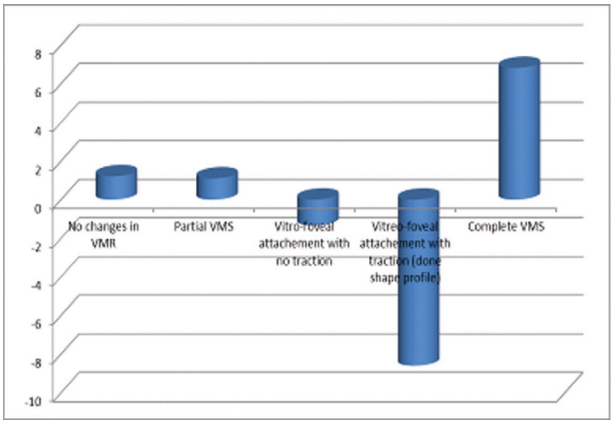
An example of category 4 VMR (perifoveal vitreous detachment with traction) and multifocal DME, received 3 intravitreal Ranibizumab injections, resulted in evident improvement in CMT with complete VMS.

Figure 9



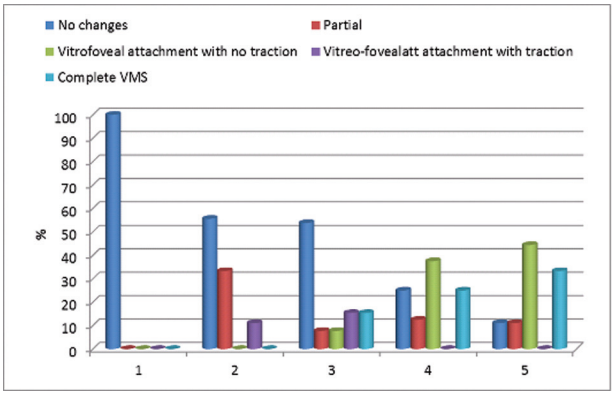
An example of category 3 VMR (perifoveal vitreous detachment with no traction) and multifocal DME, received 3 subsequent intravitreal Ranibizumab injections, resulted in poor outcome and worsening of the CMT with evolution of the VMR to perifoveal vitreous detachment with traction.

Figure 10



Influence of changes in vitreomacular relationship on visual outcome.

Figure 11



Relation between the number of injection and the outcome.

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Nil.

Conflicts of interest
None of the author's have any financial interest in any of products or techniques used.

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