IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 15, Issue 6 Ver. IV (June. 2016), PP 41-47
www.iosrjournals.org

A cross-sectional study of association between Optical Coherence Tomographic and Fluorescein Angiographic patterns in patients with Diabetic Macular Edema

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Abstract:
Purpose: *To assess the association between the features of optical coherence tomography (OCT) and fluorescein angiography (FA) in clinically significant diabetic macular edema.*
Materials and Methods: *It was an observational, cross-sectional study conducted at Upgraded Department of Ophthalmology, S.M.S Hospital and Medical College, Jaipur. It involved 181 eyes (100 patients) with clinically significant diabetic macular edema. The FA features were categorized into focal leakage type, diffuse leakage type, and diffuse cystoid leakage type. The OCT features were categorized into five types: Diffuse retinal thickness (DRT), Cystoid macular edema (CME), Serous retinal detachment (SRD), Posterior hyaloidal traction (PHT) and Tractional retinal detachment (TRD). The association between FA types and OCT types were analyzed, and their associations in terms of visual acuity, central foveal thickness and stages of diabetic retinopathy were evaluated.*
Results: *There was a significant correlation (p value < 0.000) between fluorescein angiography types and OCT types. 69% eyes with focal leakage on FA had DRT on OCT while 50 % eyes with diffuse cystoid leakage showed CME on OCT. There was also a significant association of OCT and FA patterns with the stages of diabetic retinopathy and the visual acuity. DRT on OCT and the focal leakage on FA showed the least foveal thickness and the best visual acuity (p value < .000). The foveal thickness increased and visual acuity worsened as the stages of diabetic retinopathy progressed from Mild NPDR to PDR.*
Conclusions: *There was a significant correlation between the features of OCT and fluorescein angiography in clinically significant diabetic macular edema. The analysis of diabetic macular edema based on both OCT and fluorescein angiography can provide information that may be useful to disclose the pathogenesis of the edema and to optimize the treatment for each type.*
Keywords: *Diabetic macular edema, Fluorescein angiography, Optical coherence tomography*

I. Introduction

Diabetic retinopathy (DR) is a leading cause of vision-loss globally. Of an estimated 285 million people with diabetes mellitus worldwide, approximately one third have signs of Diabetic Retinopathy (DR) and of these, a further one third have vision-threatening DR, including Diabetic macular edema (DME).[1] DME is generally defined as retinal thickening in the posterior pole, resulting from retinal vascular hyperpermeability and other alterations in the retinal microenvironment.[2] DME can occur in eyes with a wide spectrum of underlying retinopathy, from mild NPDR to PDR.

The Wisconsin Epidemiologic study of Diabetic Retinopathy reported the 10-year incidence of macular edema to be between 13.9% and 25.4%.[3] A pooled individual participant meta-analysis involving 35 studies conducted worldwide from 1980 to 2010, estimated the global prevalence of DR and vision threatening DR among patients with diabetes to be 35.4 and 7.5 % respectively.[1] Localized Macular edema is caused by focal leakage from micro aneurysms and dilated capillary segments. [4] Diffuse Macular edema is generally defined as retinal thickening measuring 1 disc area in size or greater, and shows more widespread and ill-defined leakage on fluorescein angiography caused by generalized disruption of blood retinal barrier.[5,6] Clinically significant macular Edema (CSME) as defined by ETDRS includes retinal edema located at or within 500 µm of the centre of macula, hard exudates at or within 500 µm of the centre, if associated with thickening of adjacent retina or a zone of thickening larger than 1 disc area if located within 1 disc diameter of the centre of macula.

Previously described methods of assessing DME included contact and noncontact slit-lamp biomicroscopy, indirect ophthalmoscopy, fluorescein angiography and fundus stereo photography. However, given the relative lack of ability of these methods to quantify macular edema, alternate objective methods have been applied. The introduction of optical coherence tomography (OCT) allows objective evaluation of DME. [7,8,9]

Fluorescein Angiography has been used to assess vascular leakage qualitatively in macular edema. Fluorescein leakage may be present in a region of the retina that is edematous, normal thickness, or thin, and is

therefore not synonymous with macular edema.[2] OCT can offer high-resolution cross-sectional images of the retina and quantitative measurement of the retinal thickness.[8,9] Thus the physiologic aspect of clinically significant diabetic macular edema can be assessed with fluorescein angiography, and the anatomical features of clinically significant diabetic macular edema such as the extent of thickening and the retinal layer involved can be assessed with OCT. In this era of new therapeutic modalities such as intravitreal anti-VEGF or corticosteroid injection or vitrectomy for diabetic macular edema, it seems worthwhile to classify clinically significant diabetic macular edema with fluorescein angiography and OCT and to make associations between them.

In this study we tried to determine whether there is a correlation between the features of fluorescein angiography and OCT and whether visual acuity, foveal thickness and stages of diabetic retinopathy were associated with them.

II. Materials And Methods

This was a descriptive type of observational, cross-sectional, hospital based study conducted at Upgraded Department of Ophthalmology, S.M.S Hospital and Medical College, Jaipur, India.

181 eyes of 100 patients with diabetic macular edema attending the Eye OPD were recruited. Informed consent was taken from all the participants using the consent form. All the subjects underwent a medical history including age, sex, duration of diabetes, history of any previous photocoagulation or anti-VEGF treatment and a comprehensive ophthalmic examination including BCVA estimation by Snellens visual acuity chart, indirect ophthalmoscopy and stereoscopic biomicroscopy with 90D lens to diagnose diabetic macular edema according to the criteria given by ETDRS.[9]

Our study groups included both insulin dependent and non-insulin dependent non-proliferative diabetic retinopathy and proliferative diabetic retinopathy patients. The study population had varied glycemic levels and HbA1c evaluation was not done. None of the patients in our study had undergone previous photocoagulation or received anti-VEGF injection. Such patients were excluded as these could interfere with anatomic changes at the macula and may alter the findings singularly due to disease manifestation. All the participants were subjected to imaging using Topcon Spectral Domain OCT (3D OCT – 2000, Mark II; Topcon Corporation, Tokyo, Japan) and ZEISS FF 450plus Fundus Fluorescein Angiography. The interval between OCT and fluorescein angiography examination was less than 1 month for entry into this study, and no therapeutic intervention was applied to the eyes during the interval.

2.1 OCT Classification

A classification system, modified from the Otani[7] Scheme was used. The OCT findings of macular edema were graded for the presence of specific morphological patterns:

2.1.1. Diffuse retinal thickness (DRT): Increased retinal thickness with reduced intraretinal reflectivity and expanded areas of lower reflectivity, especially in the outer retinal layers. [Fig - 2.1.1]

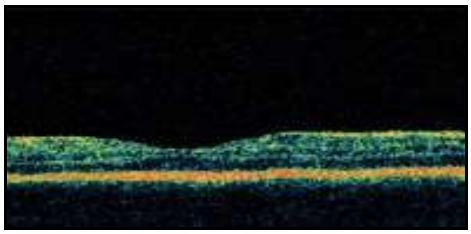

Figure – 2.1.1

2.1.2. Cystoid macular edema (CME): Localization of intraretinal cystoid-like spaces that appeared as round or oval areas of low reflectivity with highly reflective septa separating the cystoid-like cavities. [Fig - 2.1]

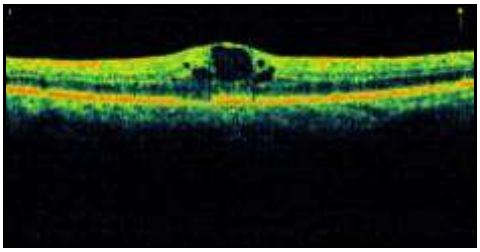

Figure – 2.1.2

2.1.3 Subretinal fluid (SRD): Accumulation of subretinal fluid (which appeared dark) beneath a highly reflective and elevation, resembling a dome, of the detached retina. The identification of the highly reflective posterior border of detached retina distinguishes subretinal from intraretinal fluid. [Fig - 2.1.3]

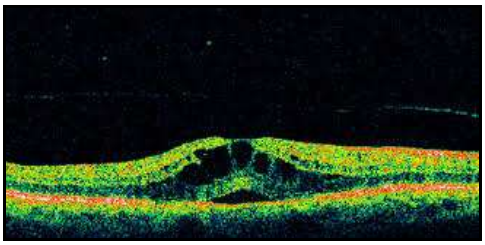

Figure – 2.1.3

2.1.4. Posterior hyaloidal traction (PHT): Highly reflective signal arising from the inner retinal surface and extending towards the optic nerve or peripherally. [Fig - 2.1.4]

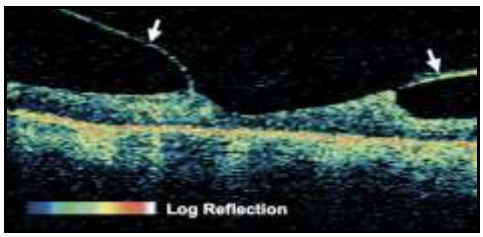

Figure – 2.1.4

2.1.5. Traction retinal detachment (TRD): Peak shaped detachment of the retina.[Fig - 2.1.5]

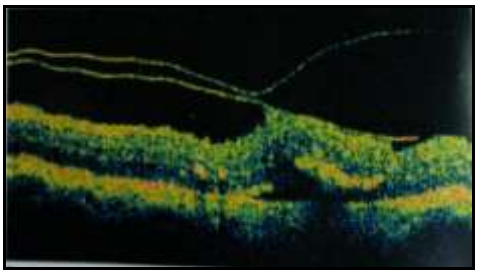

Figure – 2.1.5

When two types coexisted in one eye, the case was categorized according to the predominant type.

2.2 Fluorescein Angiography Classification

Fluorescein angiography findings were categorized into three types:

2.2.1.1. Focal leakage type, which was predominantly well defined focal areas of leakage from microaneurysm or localized dilated capillaries. [Fig - 2.2.1]

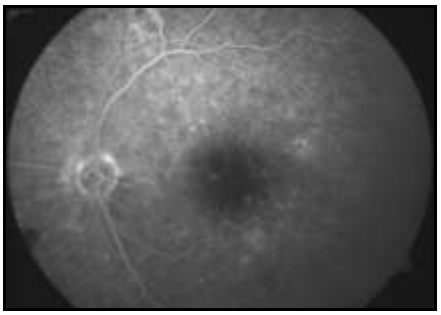

Figure – 2.2.1

2.2.2. Diffuse leakage type, predominantly widespread and ill-defined leakage involving the whole circumference of the fovea. [Fig - 2.2.2]

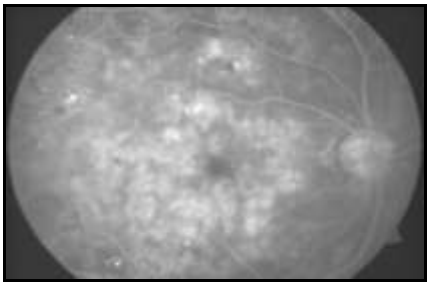

Figure – 2.2.2

2.2.3.**Diffuse cystoid leakage type**, predominantly diffuse leakage but with pooling of dye in the cystic spaces of the macula in the late phase. [Fig - 2.2.3]

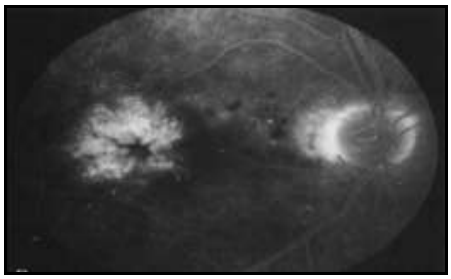

Figure – 2.2.3

Optical coherence tomography and fluorescein angiography typing in each case of clinically significant macular edema was done separately in a double-masked manner. The stages of diabetic retinopathy were classified into four groups: mild nonproliferative diabetic retinopathy, moderate nonproliferative diabetic retinopathy, severe nonproliferative diabetic retinopathy, and proliferative diabetic retinopathy based on ETDRS classification. The best-corrected visual acuity and central foveal thickness were also compared among the five OCT types, the three fluorescein angiography types, and the four stages of diabetic retinopathy.

Statistics - We have evaluated our data by means of cross tab in number and percentage. The $\chi 2$ test has been applied to assess the possible relation between fluorescein angiography types and OCT types. In quantitative data, mean and standard deviation (SD) have been calculated. A probability value (P value) less than 0.05 was considered significant.

III. Observations And Results

Sixty Six men (119 eyes) and 37 women (62 eyes) were included in this study. The age of patients ranged from 20 to 87 years ([mean ± standard deviation (SD)] 59.88 ± 11.76). The characteristics of the study population are shown in Table 1. The duration of diabetes was 11.25 ± 7.45 years. The logarithm of the minimal angle of resolution logMAR visual acuity was 0.535 ± 0.264, and central retinal thickness was 351.02 ± 110.50 µm.

Table 1 – Demographics of patients with Diabetic Macular Edema

	Minimum	Maximum	Mean	Std. Deviation
Age (years)	20	87	59.88	11.76
Diabetic since (years)	.5	30.0	11.254	7.44
logMAR values of BCVA	.10	1.00	.5348	.26
Central Foveal Thickness (µm)	241	807	351.02	110.5

The distribution of fluorescein angiography types and OCT types is shown in Tables 2 and 3.

Table 2 – Distribution of OCT Patterns among fluorescein angiography types

Fluorescei Angiography Patterns	**OCT Patterns**					**Total**	**p-value**
	DRT	**CME**	**SRD**	**PHT**	**TRD**		
Focal leakage	54	20	4	0	0	78 (43.1%)	.000
Percentage	69.2%	25.6%	5.1%	.0%	.0%		
Diffuse leakage	24	24	25	2	2	77 (42.5%)	
Percentage	31.2%	31.2%	32.5%	2.6%	2.6%		
Diffuse Cystoid leakage	4	13	9	0	0	26 (14.4%)	
Percentage	15.4%	50.0%	34.6%	.0%	.0%		
Total						181	

Focal leakage was found in 78 eyes (43.1%), Diffuse leakage in 77 eyes (42.5%) and Diffuse cystoid leakage in 26 eyes (14.4%). The OCT examination revealed DRT in 82 eyes (45.3%), CME in 57 eyes (31.5%), SRD in 38 eyes (21.0%), PHT and TRD, each in 2 eyes (1.1%). Sixty nine percent of the eyes with focal leakage on fluorescein angiography were classified into DRT on OCT, and on 65.9% of the eyes with DRT were classified into focal leakage. Conversely, the distribution of OCT patterns in eyes with diffuse leakage on fluorescein angiography was uniform with 32.5% as SRD, 31.2 % as DRT, 31.2% as CME. The incidence of diffuse leakage was 100% in eyes with PHT and TRD each, though these patterns were found in only four eyes (two eyes showing each pattern). Fifty percent of the eyes with diffuse cystoid leakage on fluorescein angiography showed CME pattern on OCT and SRD had a share of 34.6%. To summarize, focal leakage on fluorescein angiography was closely related to DRT on OCT while diffuse cystoid leakage was closely related to CME on OCT.

The proportion of eyes with focal leakage decreased as the OCT type changed from DRT to CME and SRD types. The proportion of eyes with diffuse cystoid leakage increased among the eyes with SRD and CME types on OCT.

Table 3 – Distribution of Fluorescein Angiography Patterns among OCT types

OCT Patterns	**Fluorescein Angiography Patterns**				**P value**
	Focal	**Diffuse**	**Diffuse cystoid**	**Total**	
DRT	54	24	4	82 (45.3%)	0.000
Percentage	65.9%	29.3%	4.9%		
CME	20	24	13	57 (31.5%)	
Percentage	35.1%	42.1%	22.8%		
SRD	4	25	9	38 (21.0%)	
Percentage	10.5%	65.8%	23.7%		
PHT	0	2	0	2 (1.1%)	
Percentage	0%	100%	0%		
TRD	0	2	0	2 (1.1%)	
Percentage	0%	100%	0%		
Total Count				181	

The distribution of OCT and FA patterns according to the stages of Diabetic Retinopathy was found to be statistically significant ($P < 0.000$). DRT was the most common OCT pattern found in mild and moderate NPDR. SRD was the most common pattern found in eyes with severe NPDR whereas CME was the most common pattern found in eyes with Proliferative diabetic retinopathy (PDR). Likewise, focal leakage on fluorescein angiography was the most frequent pattern in eyes with mild and moderate non-proliferative diabetic retinopathy (NPDR), while diffuse leakage on fluorescein angiography was most frequently seen in eyes with severe NPDR and proliferative diabetic retinopathy.

Table 4 - Basic Characteristics of eyes with Different OCT and FA Patterns

OCT Patterns	**Age (years)**	**Duration of Diabetes (years)**	**Visual Acuity (logMAR)**	**Central Foveal Thickness (µm)**
Diffuse Retinal Thickness (DRT)	58.65 ± 11.43	12.01 ± 7.37	0.39 ± 0.22	283.83 ± 50.40
Cystoid Macular Edema (CME)	61.72 ± 10.24	10.54 ± 6.86	0.58 ± 0.23	378.05 ± 109.02
Serous Retinal Detachment (SRD)	61.21 ± 13.22	11..45 ± 8.39	0.74 ± 0.21	436.18 ± 99.63
Posterior Hyaloidal Traction (PHT)	46.00 ± 2.83	0.75 ± 0.35	0.85 ± 0.21	407.50 ± 174.66
Tractional Retinal Detachment (TRD)	47.00 ± 29.70	7.50 ± 0.71	0.90 ± 0.14	661.00 ± 206.46
FA Patterns				
Focal leakage	59.05 ± 11.12	11.07 ± 6.85	0.40 ± 0.22	295.33 ± 62.06
Diffuse leakage	59.77 ± 12.70	11.44 ± 8.0	0.63 ± 0.25	385.74 ± 124.14
Diffuse cystoid leakage	62.73 ± 10.64	11.23 ± 7.71	0.65 ± 0.23	415.27 ± 107.31

Best-corrected visual acuity (logMAR) and central foveal thickness were analyzed according to the types of OCT and fluorescein angiography examination (Table 4). Eyes with focal leakage and with DRT on OCT had the best visual acuity and the least degree of central foveal thickening. In addition, eyes with diffuse

cystoid leakage on FA and TRD on OCT had the worst visual acuity and more central foveal thickening. [Figures 3.1 and 3.2]

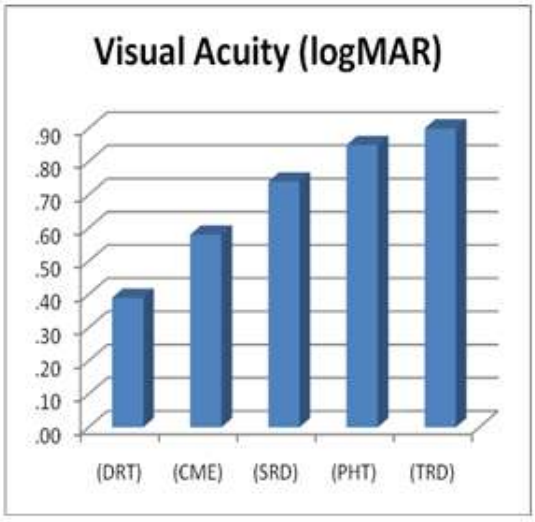

Figure 3.1

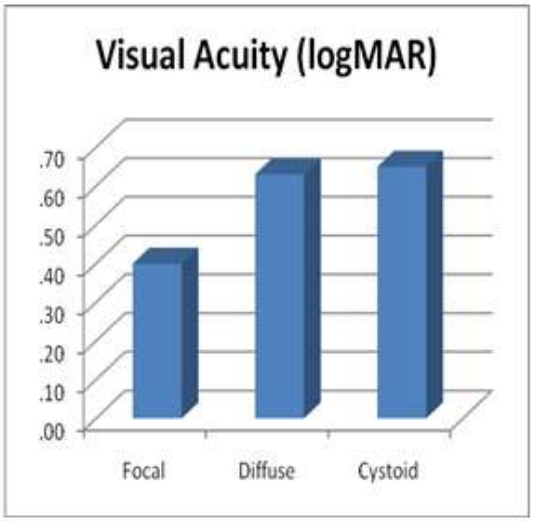

Figure 3.2

There was a significant difference in the visual acuity and central foveal thickness according to the stages of diabetic retinopathy. Best visual acuity and least foveal thickness were seen in cases with mild NPDR. The visual acuity decreased as the stages progressed to moderate and severe NPDR and PDR and the central retinal thickness increased from mild NPDR to PDR.

IV. Discussion

Macular edema is clinically defined as any increase of water in the retinal tissue resulting in an increase in foveal thickness. The diagnosis and the management of diabetic macular edema depend on traditional techniques such as stereoscopic biomicroscopy and fluorescein angiography. Fluorescein angiography is an imaging modality that has been used to identify areas of vascular leakage, and it is a kind of qualitative and functional study. The prevalence of fluorescein angiographic patterns in our study was 43.1% with focal leakage, 42.5% with diffuse leakage, and 14.4% with diffuse cystoid leakage. Optical coherence tomography is an imaging technique that produces high-resolution cross-sectional images of the retina, and it offers a structural and quantitative analysis of clinically significant diabetic macular edema.[8,10] In our study, the distribution of OCT patterns was DRT in 45.3% eyes, CME in 31.5% eyes, SRD in 21.0% eyes, PHT and TRD, each in 1.1% eyes.

A study on Optical coherence tomography imaging of macular edema by Brian Y. Kim et al[11] mentions the prevalence of five OCT patterns to be 97% for DRT, 55% for CME, 7% for SRD, 12.7% for PHT without TRD and 2.9% for PHT with TRD in their study. Similar results have been reported by Otani and Yamamoto, who showed that the most common OCT finding in DME was DRT with prevalence of 88% and 60%, respectively.[7,12] All these studies also agree that there is a correlation between retinal thickness and visual acuity in patients with DME. The results of our study indicated that visual acuity correlated significantly not only with foveal thickness but also with OCT types and fluorescein angiography types.

Eyes with focal leakage and with DRT on OCT had the best visual acuity and the least degree of central foveal thickening. In addition, eyes with diffuse cystoid leakage on FA and TRD on OCT had the worst visual acuity and more central foveal thickening. The proportion of focal leakage type decreased as diabetic retinopathy progressed. This relation came out to be statistically significant in our study ($P < 0.000$). That suggests that the large extent of ischemia in the eyes with proliferative diabetic retinopathy also involves the macular area and releases endogenous vascular permeability factors, then breaks down the blood retinal barrier, and finally causes severe and diffuse leakage from damaged capillaries. In patients with DME associated with PHT, a macular traction detachment may not necessarily have to be present to result in significant visual consequences. The traction produced by the vitreomacular interface has been postulated to play a role in the development of DME.[5,13,14]

Statistically significant association was found between the OCT and FA patterns with the stages of diabetic retinopathy ($P = 0.000$). Diffuse Retinal thickness (DRT) was the most common OCT pattern found in mild (88.6%) and moderate (58.2%) NPDR. SRD was the most common type found in eyes with severe NPDR, contributing upto 50% of the cases whereas, CME was the most common pattern found in eyes with

proliferative diabetic retinopathy (42.2%). The focal leakage type on fluorescein angiography was the most frequent pattern in eyes with mild and moderate Non-proliferative diabetic retinopathy (NPDR), while diffuse leakage type on fluorescein angiography was most frequently seen in eyes with severe NPDR and proliferative diabetic retinopathy.

V. Conclusion

In the present study, there was a significant correlation between the features of OCT and fluorescein angiography in clinically significant diabetic macular edema. The results of our study also indicated that visual acuity correlated significantly with foveal thickness as well as with OCT types and fluorescein angiography types.

Fluorescein angiography is the technique imaging neovascularization and microaneurysms but it is an invasive intervention with potential systemic side effects. OCT shows the distribution of retinal morphologic alterations in a highly reproducible manner, and is a noninvasive modality. However, the structural tomography is capable of showing only retinal pathomorphologic features and not pathophysiologic features, such as leakage phenomena where fluorescein angiographic evaluation comes handy. Hence, the clinical findings of these two diagnostic tools are complementary to each other. Knowing the consistency of these two imaging techniques with respect to the specific retinal alterations, FA could be avoided, for example, during follow-up examinations, and the role of OCT can gain clinical importance.

Because there is the limitation of cross-sectional nature in our study, further longitudinal study for this issue would be worthwhile. In summary, our study revealed a significant correlation between the features of OCT and fluorescein angiography in diabetic macular edema. These findings imply that diabetic macular edema is a broad spectrum of disease and that its treatment should be diversified according to the subtypes of macular edema. The analysis of diabetic macular edema based on both OCT and fluorescein angiography can provide information that may be useful to disclose the pathogenesis of the edema and to optimize the treatment for each type.

References

[1] Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al, Global prevalence and major risk factors of diabetic retinopathy, *Diabetes Care, 35(3)*, 2010, 556–64.

[2] Stephen J Ryan, *Retina* (China: Elsevier-Saunders, 2013)

[3] Klein R, Klein BE, Moss SE, Cruickshanks KJ, The Wisconsin Epidemiologic Study of Diabetic Retinopathy XV, The long term incidence of macular edema, *Ophthalmology, 102*, 1995, 7–16.

[4] Jack J Kanski, Brad Bowling, *Clinical Ophthalmology* (China: Elsevier-Saunders, 2011)

[5] Lewis H, Abrams GW, Blumenkranz MS, Campo RV, Vitrectomy for diabetic macular traction and edema associated with posterior hyaloidal traction, *Ophthalmology, 99*, 1992, 753–759.

[6] Sander B, Larsen M, Moldow B, Lund-Andersen H, Diabetic macular edema: passive and active transport of fluorescein through the blood-retina barrier, *Invest Ophthalmol Vis Sci, 42*, 2001, 433–438.

[7] Otani T, Kishi S, Maruyama Y, Patterns of diabetic macular edema with optical coherence tomography, *Am J Ophthalmol, 127*, 1999, 688–693.

[8] Hee MR, Puliafito CA, Wong C, et al, Quantitative assessment of macular edema with optical coherence tomography, *Arch Ophthalmol, 113*, 1995, 1019–1029.

[9] Yang CS, Cheng CY, Lee CF, Hsu WM, Liu JH, Quantitative assessment of retinal thickness in diabetic patients with and without clinically significant macular edema using optical coherence tomography, *Acta Ophthalmol Scand, 79*, 2001, 266–270.

[10] Sanchez-Tocino H, Alvarez-Vidal A, Maldonado MJ, Moreno-Montanes J, Garcia-Layana A, Retinal thickness study with optical coherence tomography in patients with diabetes, *Invest Ophthalmol Vis Sci, 43*, 2002, 1588–1594.

[11] Brian Y. Kim, Scott D. Smith D, Optical Coherence Tomographic Patterns of Diabetic Macular Edema, *Am J Ophthalmol, 142*, 2006, 405–412.

[12] Yamamoto S, Yamamoto T, Hayashi M, et al, Morphological and functional analyses of diabetic macular edema by optical coherence tomography and multifocal electroretinograms, *Graefe's Arch Clin Ophthalmol, 239*, 2001, 96 –101.

[13] Nasrallah FP, Jalkh AE, Van Coppenolle F, et al, The role of the vitreous in diabetic macular edema, *Ophthalmology, 95*, 1988, 1335–1339.

[14] Hikichi T, Fujio N, Akiba J, et al, Association between the short-term natural history of diabetic macular edema and the vitreomacular relationship in type II diabetes mellitus, *Ophthalmology, 104*, 1997, 473– 478.