• Clinical Research •

Evaluation of systemic risk factors in different optical coherence tomographic patterns of diabetic macular edema

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Abstract

• AIM: To elucidate the relationship between systemic risk factors and different patterns of diabetic macular edema (DME) determined with optical coherence tomography (OCT).

• METHODS: In this cross-sectional study, DME was classified by OCT as diffuse retinal thickness (DRT), cystoid macular edema (CME) and serous retinal detachment (SRD) and the relationship between the systemic risk factors and DME patterns was evaluated.

• RESULTS: Of the 57 patients with DME, 21 (36.8%) had DRT, 24 (42.1%) had CME and 12 (21.0%) had SRD. Micro- or macro-albuminuria was significantly higher in the DRT pattern (61.9%) compared with the SRD (50.0%) and CME patterns (25.0%; *P*=0.040). Hemoglobin A1c (HbA1c) level was significantly higher and patients were younger in the DRT pattern group (*P*=0.034, *P*=0.032). Best corrected visual acuity was the worst and central macular thickness was the thickest in the CME pattern group.

• CONCLUSION: Micro- or macro-albuminuria may be more frequent and HbA1c level may be higher in patients with DRT. These patients are also seen to be younger than patients with non-DRT.

• KEYWORDS: cystoid macular edema; diabetic macular edema; diffuse retinal thickness; optical coherence tomography; serous retinal detachment

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INTRODUCTION

Diabetic macular edema (DME) remains a major cause of visual loss in patients with diabetes mellitus[1]. Its complex and multifactorial pathogenesis has not yet been fully understood. What is apparent is that the multifactorial disruption of inner and outer blood-retinal barriers leads to abnormal inflow of fluid into the neurosensory retina exceeding the outflow, resulting in intraretinal and subretinal fluid accumulation[2-5].

Optical coherence tomography (OCT) is a high-resolution and non-invasive imaging technique that permits cross-sectional images of the retina to be obtained. The axial resolution range of 5-7 μm of OCT provides information similar to that obtained from optical biopsy[6]. OCT has specifically been used for characterisation of the morphological features of DME, and three OCT patterns have been described: diffuse retinal thickening (DRT), cystoid macular edema (CME) and serous retinal detachment (SRD)[7-13]. Although the pathophysiology of these patterns has been studied previously, to the best of our knowledge, only a few studies have evaluated the association of systemic factors in different OCT patterns of DME[14-17].

In this study, the macular OCT findings of patients with DME were evaluated to determine whether specific OCT patterns are related to any systemic factors.

SUBJECTS AND METHODS

This study was designed as a cross-sectional study and conducted between January 2011 and June 2012. Approval for the study was granted by the Local Ethics Committee of Dokuz Eylul University (Protocol number: 572GA). Patients who presented at the Endocrinology Outpatient Clinic of Dokuz Eylul University Hospital and voluntarily agreed to participate in the study, were directed to the Ophthalmology Department of this hospital for ophthalmic examination. Written informed consent was obtained from all the patients complying with the research protocol and the Declaration of Helsinki was strictly followed throughout the study.

Participants were at least 18 years old with type 1 or type 2 diabetes. Age, gender, body mass index (BMI), duration and type of diabetes mellitus, severity of diabetic retinopathy (DR), if present, history of any associated systemic disease such

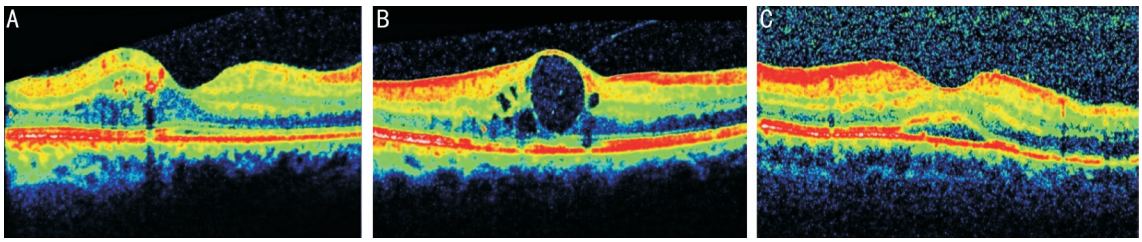

Figure 1 Different OCT patterns of DME A: Diffuse retinal thickening; B: Cystoid macular edema; C: Serous retinal detachment with mild retinal thickening.

as hypertension, hyperlipidemia, neuropathy, cardiovascular disease, details of systemic medications, alcohol and smoking habits, history of ocular surgeries including cataract surgery were recorded. BMI was calculated using the formula of weight (kg) / height squared (m^2).

After fasting overnight, blood samples of the patients were taken between 8:00 and 9:00 a.m. The following parameters were measured: creatinine, serum total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides (TG), hemoglobin A1c (HbA1c), serum albumin and 24-hour urinary albumin excretion. The patients were divided into groups of normo-albuminuria (<30 mg/24h), micro-albuminuria (30-299 mg/24h) and macro-albuminuria (≥300 mg/24h) according to the amount of albumin excreted in the urine in 24h[18]. Patients were not included if the serum albumin levels were not within normal limits as albumin is a negative phase reactant.

In addition to a complete ophthalmic examination [best corrected visual acuity (BCVA) measured with a Bailey-Lovie chart, applanation tonometry, slit-lamp biomicroscopy, lens evaluation and dilated posterior pole examination], spectral-domain OCT (Heidelberg Retinal Angiography-Optical Coherence Tomography-II, Germany) was performed in all eyes. Of 6 shots were lined up with the radial line scan at an angle of 30° to each other. The eyes with clinically significant macular edema as defined by ETDRS, and with central macular thickness (CMT) on OCT≥250 μm attributable to DME were studied[19]. Three patterns of DME were categorized according to the cross-sectional images in OCT by three retinal specialists (Kaynak S, Kocak N and Karahan E): 1) the DRT pattern was characterized by a sponge-like retinal swelling of the macula with reduced intraretinal reflectivity; 2) the CME pattern was characterized by intraretinal cystoid spaces of low reflectivity with highly reflective septa separating cystoid-like cavities in the macular area; 3) the SRD pattern was characterized by a shallow elevation of the retina, with an optically clear space between the retina and the retina pigment epithelium (RPE; Figure 1). If DRT was combined with CME or SMD, then it was classified as either CME or SRD, and if all patterns were combined, it was classified as SRD[20-21]. One eye of each patient was included. If both eyes of the same patient had the same pattern, the eye with higher CMT on OCT was included and if one of the eyes had DRT or CME and the fellow eye had SRD, the eye with SRD was included and if one of the eyes had DRT and the fellow eye had CME, the eye with CME was included for evaluation.

Table 1 Combinations of different optical coherence tomographic patterns of diabetic macular edema

Optical coherence tomographic patterns	*n* (%)
DRT	
DRT alone	21 (36.84)
CME	
DRT+CME	24 (42.10)
SRD	
DRT+SRD	6 (10.53)
DRT+CME+SRD	6 (10.53)
Total	57 (100)

CME: Cystoid macular edema; DRT: Diffuse retinal thickness; SRD: Serous retinal detachment.

Eyes which had received panretinal scatter photocoagulation within the prior 4mo, yttrium-aluminum-garnet capsulotomy within the prior 2mo, or major ocular surgery including cataract extraction within the prior 6mo and eyes with an ocular abnormality other than DME (vitreomacular traction, epiretinal membrane, media opacities interfering with the reliability of OCT imaging, uveitis *etc*.) were excluded from the study.

All data were analyzed using SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA). The Pearson χ^2 test was used for comparative analyses of categorical variables. Kruskal-Wallis test was used to analyze changes in continuous variables among the three groups. For all statistical tests, a value of $P<0.05$ was considered statistically significant.

RESULTS

A total of 409 patients meeting the inclusion criteria were evaluated and 57 eyes of 57 patients were diagnosed as DME. DRT pattern was present in 21 (36.8%) eyes, CME in 24 (42.1%) and SRD in 12 (21.0%). Combinations of different OCT patterns of DME are summarized in Table 1. The mean age of the 57 patients was 58.00±11.06y, 33 patients were male and there was no significant difference between the three patterns in respect of age and gender. A total of 53 patients with DME were diagnosed with type 2 diabetes and

Table 2 Characteristics of the patients mean±SD

Characteristics	Diffuse retinal thickening (*n*=21)	Cystoid macular edema (*n*=24)	Serous retinal detachment (*n*=12)	Total (*n*=57)	*P*
Age (y)	53.90±10.80	60.92±10.25	59.33±11.77	58.00±11.06	0.115
Gender (M/F)	13/8	14/10	6/6	33/24	0.800
Type of diabetes mellitus (Type 1/Type 2)	3/18	0/24	1/11	4/53	0.170
Insulin (N/Y)	6/15	6/18	1/11	13/44	0.389
Duration of diabetes (y)	17.95±9.19	14.08±7.51	18.83±5.97	16.50±8.04	0.124
Body mass index (kg/m^2)	28.09±5.37	30.11±6.92	28.62±4.05	29.05±5.83	0.441
Smoking (N/Y)	16/6	20/4	10/2	46/11	0.805
Alcohol (N/Y)	19/2	22/2	11/1	52/5	0.988
Hypertension (N/Y)	7/14	10/14	3/9	20/37	0.600
Cardiovascular disease (N/Y)	17/4	19/5	8/4	44/13	0.614
Micro- or macro-albuminuria (N/Y)	7/14	7/17	4/8	18/39	0.946
Hemoglobin A1c (%)	9.01±1.95	8.15±1.76	7.53±1.52	8.33±1.84	0.032[a]
Creatinine (mg/dL)	1.09±0.54	0.94±0.33	1.68±1.58	1.15±0.85	0.299
Total cholesterol (mg/dL)	192.05±34.29	197.37±49.63	176.75±40.71	191.07±42.65	0.517
Triglycerides (mg/dL)	177.00±78.26	158.92±89.86	167.58±77.74	167.40±82.20	0.588
HDL cholesterol (mg/dL)	40.38±13.69	41.42±10.50	37.50±10.04	40.21±11.59	0.705
LDL cholesterol (mg/dL)	119.24±29.67	122.25±36.70	102.75±34.46	117.03±34.03	0.301
Anti-hyperlipidemia drugs (N/Y)	18/3	20/4	9/3	47/10	0.731

HDL: High-density lipoprotein; LDL: Low-density lipoprotein; N: No; Y: Yes. [a]*P*<0.05.

Table 3 Ophthalmic features of the eyes in different patterns of diabetic macular edema mean±SD

Ophthalmic features	Diffuse retinal thickening (*n*=21)	Cystoid macular edema (*n*=24)	Serous retinal detachment (*n*=12)	Total (*n*=57)	*P*
Best corrected visual acuity	0.62±0.31	0.36±0.26	0.44±0.30	0.47±0.31	0.024[a]
History of cataract surgery (N/Y)	15/6	20/4	10/2	45/12	0.568
Intraocular pressure (mm Hg)	15.48±3.29	15.42±2.65	16.08±2.78	15.58±2.89	0.792
Central macular thickness (μm)	313.6±94.7	593.7±165.3	394.4±134.8α	448.5±185.6	0.000[b]
DR stage					0.450
Mild-moderate NPDR	6	8	6	20	
Severe NPDR-PDR	15	16	6		
Previous treatment					0.091
None	12	8	9	29	
Focal/grid laser	6	12	2	20	
Intravitreal anti-VEGF/steroid/combined	1	4	1	6	
Combined laser+intravitreal VEGF/steroid	2	0	0	2	
PPV	0	0	0	0	

NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; PPV: Pars plana vitrectomy; VEGF: Vascular endothelial growth factor; N: No; Y: Yes. [a]*P*<0.05; [b]*P*<0.001.

the mean duration of diabetes was 16.50±8.04y. The patient characteristics are summarized in Table 2.

Of the systemic factors, micro- or macro-albuminuria was seen at a statistically significantly higher rate in patients with DRT and 61.9% of the patients with DRT had macro- or microalbuminuria (*P*=0.040). The HbA1c level was statistically significantly different between the different patterns of DME (*P*=0.032) but in post-hoc analysis, there was no statistical significance. The HbA1c level was significantly higher in DRT compared to non-DRT (*P*=0.034). In regression analysis after controlling age, duration of diabetes, hypertension, cardiovascular disease and grade of DR, neither HbA1c nor micro- or macro-albuminuria had a significant effect on 3 different OCT patterns of DME.

The ophthalmic features of the eyes in different OCT patterns are summarized in Table 3. Eyes with a DRT pattern showed statistically significantly better BCVA than those with CME pattern. In the post-hoc analysis, the DRT and SRD patterns demonstrated significantly thinner CMT values compared with the CME pattern.

DISCUSSION

DME is the leading cause of visual impairment and blindness among patients with diabetes mellitus. Since the Early Treatment Diabetic Retinopathy Study established the efficacy of laser photocoagulation, that has been the standard treatment for DME. Recently, several studies have reported the effectiveness of anti-vascular endothelial growth factors (anti-VEGFs) and intravitreal administration of these agents has become more widespread[22-26]. However, it has been observed that the responses to these treatments are very variable and unpredictable. Some authors have suggested that DME patterns determined by OCT may be associated with the response to the treatment strategies[21,27]. On the basis of this, it can be suggested that a better understanding of the systemic risk factors that influence the morphology of the macula in DME would help predict treatment outcome. To the best of our knowledge, only a few studies have evaluated the association of systemic factors in different OCT patterns of DME[15-17]. However, in a study by Ghosh *et al*[17] female diabetic patients were not evaluated and only cases with SRD were studied by Gupta *et al*[15].

In this study, DRT occurred in all the patterns of DME. Interstitial flow of fluid as managed by Müller cells may occur in the retina and can be seen as the DRT pattern in OCT images[28]. Subsequently, intrastoplasmic swelling of the Müller cells results in liquefaction necrosis that may leads to CME which was present in 30 (52.6%) eyes in our study. A total of 12 (21.0%) patients had SRD resulting from an abnormality in draining of the vascular system and an impairment in the function of the RPE (SRD; Table 1). These frequencies of the patterns are consistent with the reports of previous studies[7,13,20-21,27].

Table 2 depicts the comparison of systemic factors associated with the OCT patterns of DME. Although there was no significant difference in age between the three groups, patients with DRT were significantly younger than the patients with non-DRT, when the groups were compared binary as DRT and non-DRT (CME+SRD; P=0.032). DRT may be the earlier finding of DME compared with CME and SRD. No difference was determined between the 3 groups in terms of type of diabetes, insulin usage and duration of diabetes mellitus.

Previous studies have shown variations in the relationship between DME and nephropathy. Aiello *et al*[29] demonstrated a positive relationship and reported that dialysis may reverse macular edema in some patients. In another study, Klein *et al*[30] found no relationship between gross proteinuria and macular edema over a 10-year period while controlling for other factors. In terms of DME patterns, Koo *et al*[31] reported that the SRD pattern was more frequent in patients with albuminuria. In the present study, the serum creatinine level in the SRD pattern was higher than in other DME patterns, but was not statistically significant in the binary comparision of SRD and non-SRD patterns. In contrast to this result, micro- or macro-albuminuria was significantly more frequent in the DRT pattern (P=0.040). Microalbuminuria was determined in 8 (38.1%) patients and macroalbuminuria in 5 (23.8%) patients in this pattern.

HbAlc level is the indicator of glycemic control and high levels significantly increase the rate of DME, while a reduction of HbA1c levels with tight glycemic control decreases the rates of macular edema and other microvascular complications[32-35]. Turgut *et al*[32] reported that the levels of HbA1c were higher in patients with SRD associated with CME compared to those with only CME. In contrast to these findings, current study patients with DRT were determined to have significantly high HbA1c levels. This could have been due to an initial breakdown of the inner blood retinal barrier caused by impaired glycemic control. The pathogenesis of DRT involves the persistent breakdown of this barrier, resulting from the loss of anchor proteins in the tight junctions in the capillary endothelial cells[36]. The glycemic regulation in patients with DRT may be not fully controlled in the early period. Also, younger age may also affect diabetic patient compliance. The CME and SRD patterns are expected to affect the macula pathophysiologically later. However, in these patients previous glycemic control is also important in addition to the present systemic findings. Furthermore, the response of the macula against systemic factors and the DME patterns to form are still unpredictable. This response, which varies from patient to patient, may be due to some still unexplored features of the macula.

The worst BCVA values and the highest CMT values were determined in the CME group, which was consistent with previous studies[12,16]. Similarly, Yamamoto *et al*[8] reported that visual acuity was significantly worse in eyes with diabetic CME than in those with diffuse retinal swelling with no cystoid edema.

The present study has some limitations that require consideration. The sample size was small and represents the results of a single center. Also, a longitudinal study with a control group may provide more informative results. Other OCT aspects such as external limiting membrane and the junction between the inner and outer segments of photoreceptors (ellipsoid zone) were not investigated in this study.

In conclusion, the pathogenesis of DME is still unclear and different patterns of DME might be caused by dissimilar ocular or systemic risk factors. In the light of the results of this study, it can be considered that micro- or macro-albuminuria might be more frequent and HbA1c might be higher in patients with DRT. These patients were also determined to be younger than patients with non-DRT.

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