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Relationship between Risk Factors and Patterns of Diabetic Macular Edema on Optical Coherence Tomography

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ABSTRACT:
Background: DME is an important cause of vision loss in diabetic patients with diabetic retinopathy. OCT has been widely used as a valuable tool for diagnosis and management of DME. **Objectives:**The specific objectives of the study were (1) to assess patterns of DME using SD-OCT; and (2) to compare between the OCT patterns of DME and risk factors (age, DM duration, hypertension, glycemic control, lipid profile, blood urea, serum creatinine, and smoking). **Methodology:** This is a descriptive study of 60 out-patients and in-patients with DME who presented to our centre over a period of 18 months. Patients underwent detailed ocular examination and SD-OCT was done to assess the DME patterns in patients with CSME. Baseline investigations done for evaluation of diabetic patient were utilized. Correlation between three patterns of DME, namely, SLDRT, CME, SRD and the selected risk factors was studied.**Results:** A total of 60 eyes of 60 patients were included. Mean age was 56.80±10.65 years and mean duration of diabetes was 14.70±5.60 years. Most common pattern was CME (41.67%), followed by SLDRT (36.67%) and SRD (21.67%). Highest CMT and worst VA were observed in CME pattern. Majority of the eyes had Severe NPDR and PDR. Significant differences across different patterns of DME were observed in Duration of diabetes, Hypertension, HbA1c, Blood Urea, Serum Creatinine and HDL Cholesterol. Duration of diabetes and number of hypertensive patients were highest in CME; HbA1c highest in SLDRT; Blood Urea, Serum Creatinine were highest in SRD; and HDL-C was lowest in SLDRT. **Conclusion:** A significant association was observed between the different patterns of DME and some risk factors.

Key words: Diabetic Macular Edema; Optical Coherence Tomography; Sponge-like Diffuse Retinal Thickening; Cystoid Macular Edema; Serous Retinal Detachment

I. INTRODUCTION

Diabetic retinopathy (DR) is one of the major causes of legal blindness in the working-age population around the world. A leading cause of central vision impairment among patients with DR is Diabetic Macular Edema (DME). DME is estimated to affect approximately 21 million people worldwide, with a global prevalence of 7.5 per cent.[1] More than 21 per cent is the estimated prevalence of Diabetic Retinopathy in India.[2] DME affects nearly 30 per cent of people with diabetes who have had it for more than 20 years.[3]

DME is characterized by retinal thickening, which is caused primarily by exudation from incompetent retinal capillaries in the macula. The ETDRS defined the criteria for 'clinically significant macular edema' (CSME) as having any of the following characteristics: (a) Retinal thickening at the centre of the macula, (b) Retinal thickening and/or adjacent hard exudates at or within 500 microns of the centre of the macula, and (c) Area of retinal thickening greater than or equal to 1 disc area, any part of which is within one disc diameter of the centre of the macula.[4]

DME can occur in both type 1 and type 2 DM patients. The likelihood of developing DME increases with severity of DR.[5] Longer duration of diabetes, higher systolic blood pressure (BP), high cholesterol, and higher HbA1C are some of the most important systemic risk factors for DME.[6]DME is diagnosed using slit-lamp biomicroscopy, fluorescein angiography, and, more recently, Optical Coherence Tomography (OCT). OCT, first described by Huang et al.[7] in 1991, is a non-invasive imaging modality which is capable of providing high-resolution cross-sectional images of the neurosensory retina.[8] OCT is based on low-coherence interferometry technique, in which multiple axial scans are used to produce a retinal image.[7] Spectral domain OCT (SD-OCT) helps in faster image acquisition. It also has better resolution and depth penetration.[9]

The OCT patterns of DME are generally classified into Diffuse Retinal Thickening (DRT), Cystoid Macular Edema (CME), Subretinal Detachment (SRD), and Vitreomacular Interface Abnormalities (VMIA).[10] The role of OCT has been investigated to a great extent for classification of the morphological patterns of DME. It facilitates

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in better anatomical characterization of CSME and hence is more relevant while planning management strategies, following up, explaining prognosis and predicting visual outcome. According to ETDRS, early detection and treatment of CSME by laser therapy decreases the risk of moderate visual loss by 50 per cent.[11]

Management of DME has evolved substantially since the 1980's. Laser was considered the gold standard of treatment then. Intra-vitreal injections of corticosteroids and anti-Vascular Endothelial Growth Factor (VEGF) agents have become the mainstay of DME management over the last decade.

Previous studies have shown that a particular OCT pattern of DME could be associated with specific systemic risk factors (for example, hypertension, hyperlipidemia or renal dysfunction), implying that the pathogenesis of different OCT patterns could be different.[12,13] Previous research has shown that different OCT patterns respond differently to treatments, implying that the OCT pattern may be one of the key factors in deciding the treatment modality in DME.[14,15]In this context, the present study, aiming to elucidate the correlation of different OCT patterns of DME with risk factors, is apt and timely, which would also help in early and appropriate management.

II. OBJECTIVES

The specific objectives of the study were:

1. To assess patterns of DME using SD-OCT; and
2. To compare between the OCT patterns of DME and risk factors (age, duration of DM, hypertension, glycemic control, lipid profile, blood urea, serum creatinine and smoking).

III. METHODOLOGY

The present study was a descriptive study done on 60 DME patients attending Department of Ophthalmology in a tertiary care centre during the study period of 18 months (November 2019 to May 2021). After obtaining approval and clearance from the institutional ethics committee, all out-patients and in-patients having Type 1 or Type 2 DM with DME attending ophthalmology department, satisfying the following inclusion and exclusion criteria, were enrolled in the study after obtaining informed and written consent.

Inclusion Criteria:

1. Age group: 30-65 years
2. Patient willing to give informed consent for the study
3. Both men and women who are previously diagnosed with DM with DME
4. Patients with / without Hypertension
5. Clear ocular media

Exclusion Criteria:

1. Patient not willing to give informed consent for the study
2. Media opacities (dense cataract, uveitis, etc.) interfering with the reliability of OCT imaging
3. Other causes of macular edema (ARMD, Vitreomacular traction, ERM, full thickness or lamellar Macular holes, retinal venous occlusion etc)
4. Those patients with history of prior treatment for DME (Intravitreal injection or Macular photocoagulation) or any significant eye trauma.

A detailed history including Demographic data, Diabetes type, Duration of Diabetes, Smoking habits, associated systemic disease such as Hypertension, and history of any ocular surgery or ocular trauma in the past were recorded. Detailed ocular examination was done, which included Best Corrected Visual Acuity (BCVA), slit lamp biomicroscopic examination, Intraocular Pressure (IOP) and dilated fundus examination. SD-OCT was performed to assess the patterns of DME. Baseline investigations like FBS, PPBS, HbA1c, lipid profile, blood urea, serum creatinine done for evaluation of a diabetic patient were utilized.

The eyes with CSME as defined by ETDRS, and with Central Macular Thickness (CMT) on OCT ≥250µm attributable to DME were studied. According to the cross-sectional images in OCT, three patterns of DME were included in the study, namely, Sponge like Diffuse retinal thickening (SLDRT), Cystoid macular edema (CME) and Serous retinal detachment (SRD).

One eye of each patient was included in the study. If both eyes of the same patient had the same pattern of DME, the eye with relatively higher CMT on OCT was included. If both eyes of the same patient had different patterns of DME, the eye with relatively severe DME was included. In other words, if the either eye had SLDRT or CME and the fellow-eye had SRD, the eye with SRD was included for evaluation. In our study, 17 patients (nearly 28 per cent) had bilateral involvement, and they were classified based on the aforementioned method. Sample size of 60 patients was calculated taking into account the prevalence of DME as 7% based on the previous studies. A total of 60 eyes of 60 patients were evaluated.

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After obtaining the required data, the correlation between the three patterns of DME and the selected risk factors, namely, 1) Age, 2) Duration of DM (DM-D), 3) Hypertension (HTN), 4) Smoking, 5) Glycemic control (FBS, PPBS, HbA1c), 6) Lipid profile (Total cholesterol, Serum TG's, HDL-C, LDL-C), 7) Renal function tests (Blood urea, Serum creatinine), was studied. Association of DR grades with patterns of DME, and the mean visual acuity and CMT in different patterns of DME were also studied.The data was analyzed using Descriptive Statistics, Regression Model and Kruskal-Wallis test. For all statistical tests, a p value <0.05 was considered statistically significant.

IV. RESULTS

A total of 60 eyes of 60 patients were included. The mean age of the 60 patients was 56.80±10.65 years and mean duration of diabetes was 14.70±5.60 years. Nearly 57 per cent of the total of 60 patients was males, and the remaining were females. Most common pattern was CME (41.67%), followed by SLDRT (36.67%) and SRD (21.67%) (Figure 1).

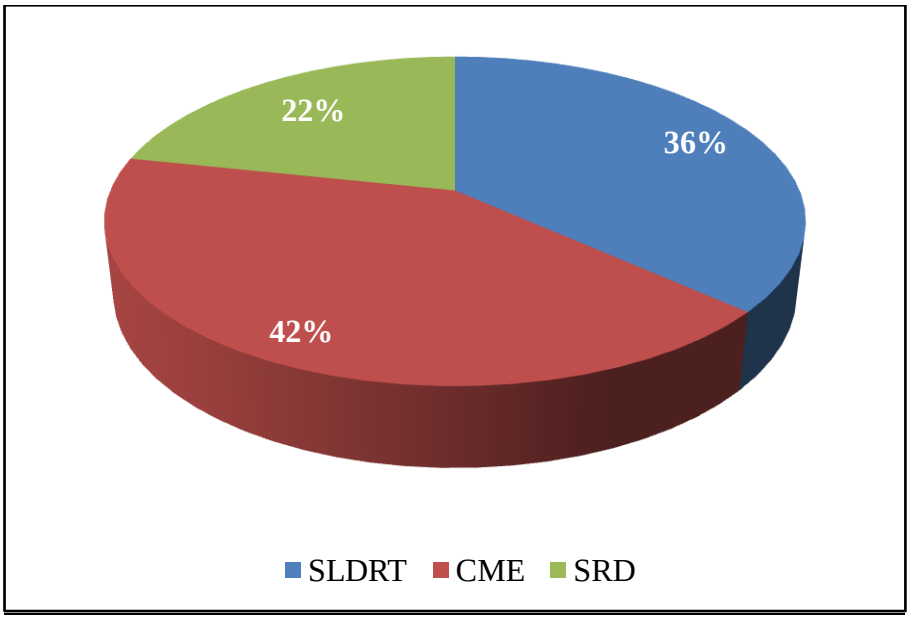

Figure 1: OCT Patterns of DME

A majority of the patients (97 per cent) belonged to Type 2 DM. A majority of the patients (40 per cent) were classified as having Severe NPDR, followed by PDR (33.33 per cent) and Moderate NPDR (26.67 per cent). Similar pattern was seen in different patterns of DME (Figure 2).

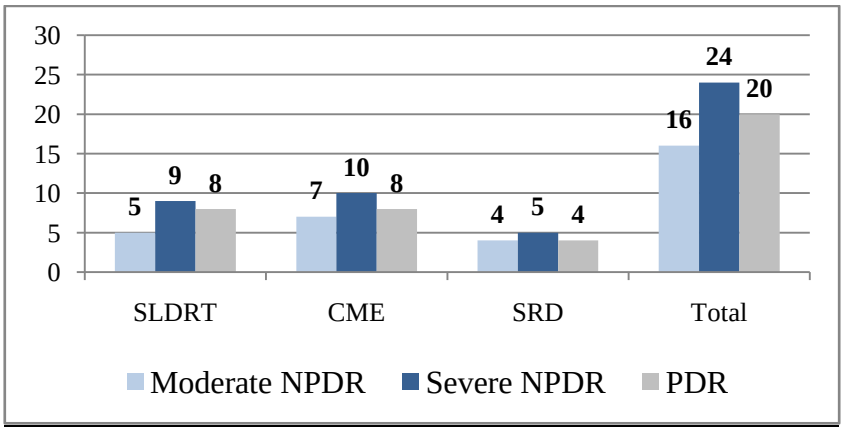

Figure 2: Association of Grades of DR with patterns of DME

The CMT varied across the patterns of DME; the mean CMT was highest in CME (520.92±97.27 µm), followed by SRD and SLDRT. The CMT of 60 patients varied from 268 to 638,

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with a mean of 451.80 µm. The worst visual acuity was observed in patients having CME (0.90±0.16), followed by SRD, while the relatively better visual acuity was found in patients with SLDRT (Table 1). As the CMT increases, visual acuity worsens. Statistically significant differences were observed in both CMT and BCVA across the three patterns of DME.

Table 1: Visual Acuity and CMT in different patterns of DME

Parameters	SLDRT	CME	SRD	Overall
CMT (µm)	380.59±59.49	520.92±97.27	439.38±84.31	451.80±102.49
BCVA (LogMAR)	0.61±0.20	0.90±0.16	0.82±0.16	0.78±0.21
Range of CMT (µm)	268 - 471	346 - 638	287 - 536	268 - 638

Among the systemic factors selected for the study, statistically significant differences across different patterns of DME were observed in Duration of diabetes, HbA1c, Blood Urea, Serum Creatinine and HDL Cholesterol. There was no significant difference amongst the three patterns in respect of age, FBS, PPBS, TC, STG and LDLC (Table 2). When the variation in the significant factors was analyzed, it could be seen that DM-D was highest in CME, followed by SRD and SLDRT. On the other hand, HbA1c was highest in SLDRT, followed by CME and SRD; while in the case of BU, SC and HDLC, it was highest in SRD, followed by CME and SLDRT.

Table 2: Association* of systemic factors with patterns of DME

(Mean±SD)

Factors	SLDRT	CME	SRD	Overall	Kruskal Wallis' H Value	p Value	Significance
Age	52.23 ±7.32	59.04 ±12.47	60.23 ±9.58	56.80 ±10.65	-2.8187	0.2443	
DM-D	12.64 ±4.35	16.44 ±5.43	14.85 ±6.94	14.70 ±5.60	-10.1876	0.0061	Significant
FBS	149.64 ±16.82	159.52 ±17.96	148.23 ±12.96	153.45 ±17.12	0.1920	0.9085	
PPBS	282.86 ±85.68	304.84 ±79.29	250.69 ±53.52	285.05 ±78.62	4.4091	0.1103	
HbA1c	9.36 ±1.38	8.51 ±1.42	7.47 ±0.66	8.60 ±1.44	8.4722	0.0145	Significant
BU	29.36 ±9.02	36.00 ±16.34	37.15 ±12.57	33.82 ±13.48	-8.6766	0.0131	Significant
SC	1.10 ±0.45	1.21 ±0.38	1.35 ±0.66	1.20 ±0.48	-28.3862	0.0000	Significant
TC	199.73 ±41.44	219.68 ±64.02	218.69 50.99	212.15 ±53.84	-1.4629	0.4812	
STG	175.73 ±52.49	232.40 ±204.83	188.00 ±77.92	202.00 ±141.33	-1.9761	0.3723	
HDLC	35.45 ±6.20	37.00 ±8.86	37.92 ±7.34	36.63 ±7.58	-17.0657	0.0002	Significant
LDLC	115.45 ±37.56	114.72 ±32.42	129.85 ±37.34	118.27 ±35.37	-2.3605	0.3072	

*Association is studied in terms of mean values of these parameters and their variation across different patterns of DME.

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More than half (56.66 per cent) of the patients had hypertension among whom, highest number of hypertensive patients was seen in CME (52.94%), followed by SLDRT (29.41%) and SRD (17.64%). Twenty five per cent of patients were smokers. However, there was not much variation in number of smokers across patterns (Figure 3).

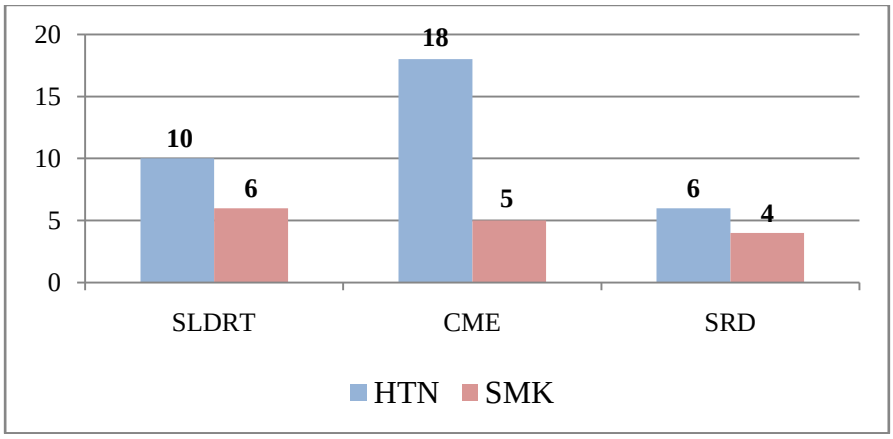

Figure 3: Association of hypertension and smoking with patterns of DME

The OCT images of three patterns of DME in our study are depicted in Figures 4, 5 and 6.

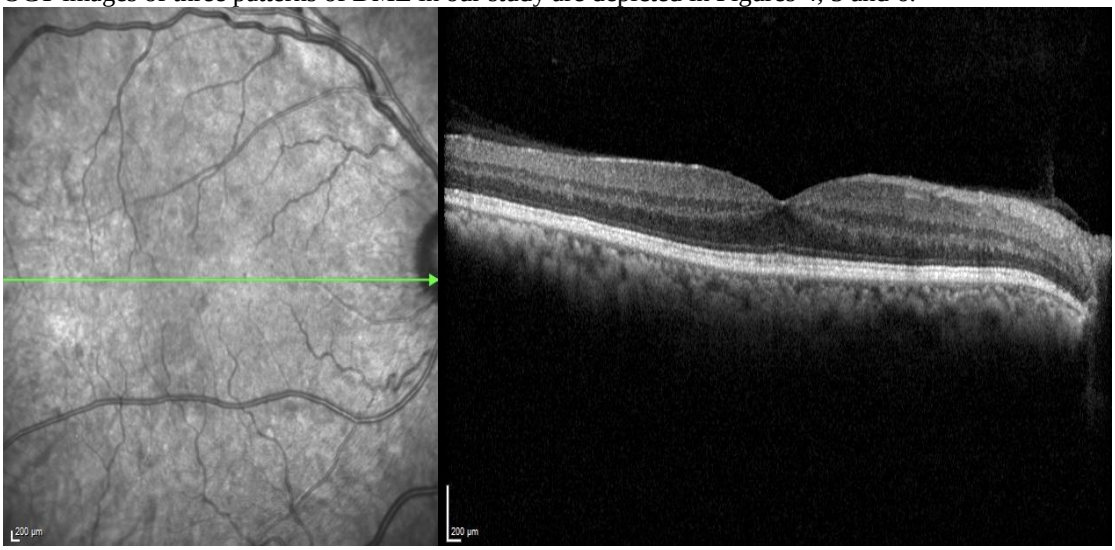

Figure 4: SD-OCT of right eye showing DRT pattern with CMT=268 µm

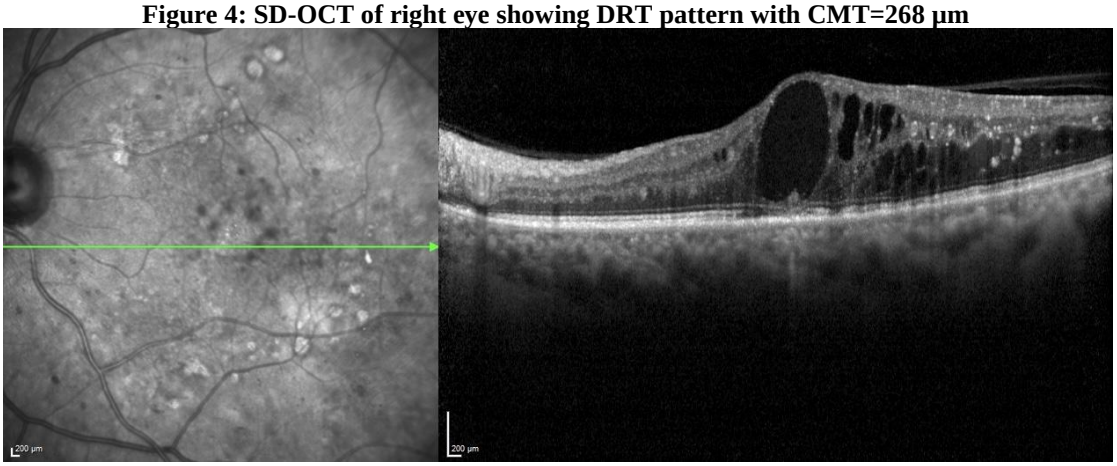

Figure 5: SD-OCT of left eye showing CME pattern with CMT=622 µm

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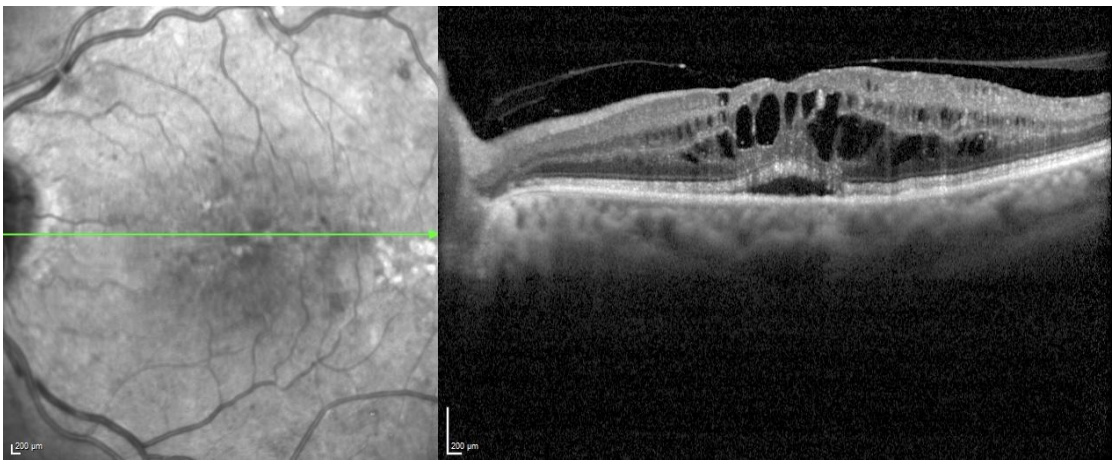

Figure 6: SD-OCT of left eye showing SRD pattern with CMT=424 µm

V. DISCUSSION

Most common OCT pattern of DME was CME, followed by SLDRT and SRD. Our results were consistent with a study conducted to elucidate the relationship between systemic risk factors and different patterns of DME determined with OCT.[16] However, there are few studies which did not conform to our study results. Ghosh et al. (2014) discovered that the most common pattern of DME was DRT, followed by SRD and CME, [12] and a study by Sanaa et al. (2019) revealed that SLDRT was the most common pattern, followed by CME and SRF.[17]

The majority of the patients were classified as having Severe NPDR and PDR. Similar pattern was seen in different patterns of DME.The major ocular risk factor associated with DME is DR severity. Although DME can be seen at any level of DR, an increasing DR severity has been associated with an increasing prevalence of DME.[18]Our study also confirms that with increasing severity of DR, the chance of occurrence of DME increases.

Our study reveals that highest CMT and worst VA were observed in CME pattern, while the relatively better visual acuity was found in patients with SLDRT. The current study was also in line with most of the previous studies regarding the effects of increased CMT on VA and supporting that the thicker the retinal layer, the greater the visual impairment.[19,10]

The mean age of the 60 patients was 56.80±10.65. Older age and tobacco smoking was found to be significant risk factors for DME.[20] The mean duration of diabetes was 14.70±5.60. Many studies, both in Type-1 and Type-2 diabetes,[21,22]found disease duration to be a significant risk factor for DR.

Of the systemic factors selected for the study, significant differences across different patterns of DME were observed in Duration of diabetes, Hypertension, HbA1c, Blood Urea, Serum Creatinine and HDL Cholesterol. In the UKPDS, an analogous, randomized clinical trial of Type-2 DM patients, it was reported that strict blood glucose control resulted in a 29% reduction in laser treatment in a follow-up period of 10 years; of the laser treatments required, 78% were for DME.[23] The WESDR found that elevated baseline HbA1c was associated with increased risk of DME.[24]

The WESDR determined that systemic hypertension increased the prevalence of DME 3-fold.[25] Multiple epidemiologic studies have identified hypertension as a risk factor for DR and DME.[26,27]Thus, along with control of glucose levels, it is important to monitor and manage hypertension in diabetic patients in order to prevent exacerbations of retinal damage and DME. Correlation of serum creatinine level, albuminuria with DME has been reported.[28]

Dyslipidemia has been implicated as an independent risk factor for vision loss and DME.[29]Among the recent studies, only the Madrid Diabetes Study determined an association between LDL-C and DR incidence.[23] The HDL-C was significantly lower in the patients with DME.[16]

VI. CONCLUSION

This study showed a significant association between the patterns of DME and some risk factors, implying that the pathogenesis of different OCT patterns could be different. Previous research has shown that different OCT patterns respond differently to treatments, implying that the OCT pattern may be one of the key factors in deciding the treatment modality in DME. As a result, by regulating the DME risk factors, the development of DME can be avoided or limited, and the response to treatment may be improved.

Hence, this study may be useful in the early and appropriate management of DME.

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