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Original Article

Evaluation and Correlation of Different Patterns of Diabetic Macular Edema with Systemic Risk Factors

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Abstract

Introduction: Diabetic macular edema (DME) is the leading cause of vision loss in patients with diabetic retinopathy. Various morphological patterns of DME have been studied based on the images of optical coherence tomography (OCT) and their risk factors have been implicated.

Aim: This study was done to evaluate and correlate morphological pattern of DME with systemic risk factors on OCT.

Materials and Methods: Five hundred consecutive diabetic patients were screened. Four morphological patterns: Diffuse retinal thickness (DRT), cystoid macular edema (CME), posterior hyaloid traction (PHT), and serous retinal detachment (SRD) were evaluated with systemic risk factors.

Results: About 14.4% patients had DME. DRT was the most common pattern identified (43.1%) followed by CME (29.2%). Mean age of patients with SRD was significantly high. Insulin users, smokers, alcoholics, female gender, and patients with higher body mass index and dyslipidemia had higher prevalence of CME pattern. Patients with SRD had significantly higher HbA1c level and altered renal function. The central macular thickness and mean total macular volume were highest in patients with CME and least in DRT pattern. The visual acuity was least affected in DRT and was most affected in CME pattern.

Conclusion: DRT was the most common morphological pattern. It was predominantly seen in males, patients with shorter duration of diabetes, and lower HbA1c levels. Female gender, insulin use, alcohol consumption, smoking, and deranged lipid profile were significant risk factors for CME. Old age, longer duration of diabetes, higher HbA1c levels, and impaired renal function significantly predisposed to SRD. The study suggests a significant correlation between increased macular volume and deterioration of vision.

Key words: Cystoid macular edema, Diabetic macular edema, Diffuse retinal thickness, Optical coherence tomography, Posterior hyaloid traction, Serous retinal detachment

INTRODUCTION

Diabetic macular edema (DME) is the leading cause of vision loss in patients with diabetic retinopathy (DR).[1] It is estimated that about 15–25% of the diabetic population have DR and everyone has the potential to develop it over a period of time.[2] The exact pathogenesis of the DME is unclear. It is apparent that chronic hyperglycemia is the trigger for inflammatory process and the release of vasoactive substances due to retinal hypoxia.[3]

Among the vasoactive substances, vascular endothelial growth factor (VEGF) plays a pivot role in the pathogenesis of DME.[4] It increases vasopermeability of vessels as a result, of which there is disruption of inner and outer retinal barriers leading to abnormal inflow of fluid into neurosensory retina. Inflammation is also shown to be involved in pathogenesis. The inflammatory process causes complement activation which brings an inflow of

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neutrophils causing endothelial damage leading to more vessel disruption.[5]

According to the early treatment DR study, clinically significant macular edema, that is, CSME is defined as thickening of retina at or within 500 mm of the center of fovea or hard exudates at or within 500 mm of the center of fovea or a zone of thickness one disk large, within 1 disk diameter of macula.

Optical coherence tomography (OCT) is a non-invasive, non-contact transpupillary imaging technique that allows cross-sectional images of retina.[6] With the scanning speed of 53,000 A-scan/sec, OCT allows the evaluation of macular thickness and vitreomacular surface by taking cross-sectional images of retina.[6] Various morphological patterns of DME have been studied based on the images of OCT, namely, diffuse retinal thickness (DRT), cystoid macular edema (CME), posterior hyaloid traction (PHT), and serous retinal detachment (SRD).[7]

The DRT is characterized by a sponge like retinal swelling with reduced intra retinal reflectivity, CME pattern is characterized by intraretinal cystoid spaces of low reflectivity with highly reflective septa separating cystoid-like cavities in the macular area, and PHT is described as a highly reflective layer from the inner retinal surface. SRD as pattern is characterized by a dome like shallow elevation of the retina, with an optically clear space between the retina and the retina pigment epithelium. Some studies in the literature have shown that the response to anti VEGF injections may vary with morphological patterns of DME which, in turn, is influenced by various systemic risk factors.[8,9]

The risk factors influencing the development of DME include age, sex, type of DM, insulin use, duration of diabetes, body mass index (BMI), consumption of alcohol and smoking, Hypertension, urine albumin levels, Hb1Ac, lipid profile, serum creatinine, and blood urea levels. The aim of the present prospective observational study was to evaluate and correlate morphological pattern of macular edema with systemic risk factors.

MATERIALS AND METHODS

After taking permission from the Institutional Ethics Committee, the study was conducted on both eyes of 500 consecutive patients of diabetes mellitus of both sexes and above the age of 18 years visiting the outpatient of Regional Institute of Ophthalmology in Northern India. Patients with history of ocular trauma or surgery, hazy ocular media, or any other associated retinal or macular pathology were excluded from the study. After recording history, a detailed physical examination, including measurement of systolic and diastolic blood pressure and calculation BMI was done. Comprehensive ocular examination of both the eyes of each patient including best-corrected visual acuity evaluation using Snellens chart, intraocular pressure measurement by applanation tonometer, slit-lamp examination, and fundus examination by both direct and indirect ophthalmoscopy using 90 D lens after dilating the pupil with commercially available phenylephrine (5%) and tropicamide drops. Optical coherence tomography of each eye was done to measure the macular characteristics using RS 330 Nidek machine.

Patients with DME on OCT were recruited in the study after taking informed consent in vernacular language while adhering to the tenets of the Declaration of Helsinki. OCT identifies the layers of retina and determines macular thickness by measuring the distance between the inner limiting membrane and the retinal pigment epithelium (RPE). The Macular Cube scan, comprising 6 mm square grid, was used to record the macular data. Each scan comprised 200 A-scans. Macular thickness map on OCT revealed central macular thickness in the center 1 mm of area and mean macular volume in three concentric rings of diameters 1, 3, and 6 mm. One eye of each patient was included for analysis. 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 and the fellow eye had CME, the eye with CME was considered, if one eye had DRT or CME and the fellow eye had PHT, the eye with PHT was included and if one eye had DRT, CME or PHT and the other eye had SRD, and the eye with SRD was evaluated.

Laboratory investigation of each patient included fasting blood sugar, HbA1c, lipid profile, blood urea, and serum creatinine and urine examination for glucose and 24 h urine for albumin levels. On the basis of amount of albumin excreted in urine in 24 h, patients were divided into three groups of normoalbuminuria (<30 g/dl), microalbuminuria (30–299 mg/dl), and macroalbuminuria (>300 mg/dl).

Statistical Analysis

Statistical analysis was done using statistics software SPSS 21, IBM, USA. Pearson's Chi-squared test was used to determine whether there is a statistically significant difference between the expected frequencies and the observed frequencies in one or more categories. *t*-test and analysis of variance analysis were used to differentiate means among the two or more groups.

RESULTS

In the present prospective observational study out of 500 diabetic patients examined, 72 (14.4%) patients with DME

were recruited in the study. About 56.9% (41) patients were male and 43.1% (31) patients were female. Their mean age was 55.72 years and mean duration of diabetes was 9.93 years. On OCT, 31 (43.06%) patients had DRT, 21 (29.17%) CME, 13 (18.06%) PHT, and 7(9.72%) patients had SRD patterns.

Mean age of patients with SRD was significantly higher than patients with DRT, CME, or PHT. Predominant morphological pattern observed in males was DRT (34.7%), while in females was CME (20.8%). Insulin users, smokers, alcoholics, and patients with higher BMI and dyslipidemia showed significantly higher prevalence of CME pattern compared to DRT, PHT, or SRD, whereas patients with SRD had significantly higher HbA1c level and altered renal function. Association of hypertension with patterns of DME was not found to be significant [Tables 1 and 2] [Figure 1].

DISCUSSION

DME is the leading cause of blindness among patients with DR. This calls for the early diagnosis and follow-up of the patients to prevent or start early treatments. In DR, Muller cells are affected as a result of which interstitial fluid accumulates in the layers of the retina which is observed as DRT pattern on OCT [Figure 2a].[10] Subsequently, the long-standing fluid accumulation gives rise to liquefactive necrosis of Muller cells leading to cystic spaces formation and is observed as CME pattern on OCT [Figure 2b].[11] The pathophysiology of PHT is thought to be due to either vitreous changes in the premacular region or due to DR causing edema and traction [Figure 2c].[7] In advanced stage of diabetes, RPE function gets impaired causing accumulation of fluid between the neurosensory retina and RPE leading to retinal detachment which is seen as SRD on OCT [Figure 2d]. Since the main pathophysiology of DME is the presence of fluid between the layers of retina, OCT makes it easy to study DME and thus classify it into different morphological patterns.

Different morphological patterns of DME on OCT can predict the outcome and response to various treatment strategies which can lead to early start of treatment and can halt the progression of DME.[8,9] Studies in the literature have classified the DME patterns differently. Kim *et al.*[7] classified DME based on OCT as DRT, CME, PHT, SRD, and traction retinal detachment (TRD). Alkuraya *et al.*[12] classified DME as sponge-like retinal swellings as type 1, CME as type 2, SRD as type 3, and vitreofoveal traction as type 4, whereas Yassin *et al.*[13] and Otani *et al.*[14] classified DME into DRT, CME, and SRD subgroups. Out of 500 patients with DM, 72 patients (14.4%) presented with DME which was similar to results seen in a study done by Wong *et al.* (16.3%)[15] and Luxmi *et al.*,[16] whereas only 7.48% of patients were found with DME in a study done by Yau *et al.*[17] Mean CMT of the study group was 413.1528

Table 1: Showing clinicodemographic data of patients

Parameters	DRT	CME	PHT	SRD	*P*-value
Age (Mean±SD)	48.55±2.71	57.52±2.73	61.85±2.54	70.71±4.82	<0.001
Male (%)	25 (34.7)	6 (8.3)	6 (8.3)	4 (5.6)	<0.002
Female (%)	6 (8.3)	15 (20.8)	7 (9.7)	3 (4.2)	<0.002
Duration of Diabetes (Mean±SD)	4.52±2.77	11.76±1.97	14.00±3.19	20.86±3.58	<0.001
Insulin Use (Yes [%])	0 (0)	14 (19.4)	5 (6.9)	3 (4.2)	<0.001
Smoking (Yes [%])	4 (5.6)	12 (16.7)	-	-	<0.001
Alcohol Use (Yes [%])	1 (1.4)	12 (16.7)	-	-	<0.001
Hypertension (Yes [%])	22 (30.6)	11 (15.3)	10 (13.9)	6 (8.3)	>0.05
Mean BMI (Mean±SD)	22.22±1.87	27.96±2.55	23.38±2.23	23.45±2.89	<0.001
HbA1c (Mean±SD)	7.19±0.76	8.56±1.04	10.09±1.76	11.53±1.35	<0.001
Total Cholesterol (Mean±SD)	157.76±33.56	270.92±52.04	186.31±63.74	173.29±31.42	<0.001
Serum Triglyceride (Mean±SD)	138.75±40.22	256.59±83.44	176.85±48.03	168.14±36.41	<0.001
Serum LDL (Mean±SD)	95.01±18.50	125.20±39.93	110.71±40.12	106.86±28.91	<0.05
Serum Creatinine (Mean±SD)	0.78±0.27	1.32±0.58	1.06±0.38	1.36±0.50	<0.001
Blood Urea (Mean±SD)	38.21±3.26	55.28±23.71	45.70±19.86	59.86±31.38	<0.05
Albuminuria-Macro	0 (0)	0 (0)	1 (1.4)	5 (6.9)	<0.001
Albuminuria-Micro	2 (2.8)	12 (16.7)	4 (5.6)	1 (1.4)	<0.001

DRT: Diffuse retinal thickness, CME: Cystoid macular edema, PHT: Posterior hyaloid traction, SRD: Serous retinal detachment

Table 2 : Macular parameters and visual acuity and its correlation with different patterns of DME

Macular parameters	DRT	CME	PHT	SRD	*P*-value
Central Macular Thickness (Mean±SD)	323.06±18.32	533.14±65.01	414.46±55.05	449.71±49.83	<0.001
Macular Volume (Mean±SD)	9.43±0.69	13.12±2.13	10.62±1.73	10.36±1.13	<0.001
Visual Acuity (logMAR) (Mean±SD)	0.34±0.074	1.21±0.40	0.59±0.06	0.77±0.07	<0.001

DRT: Diffuse retinal thickness, CME: Cystoid macular edema, PHT: Posterior hyaloid traction, SRD: Serous retinal detachment

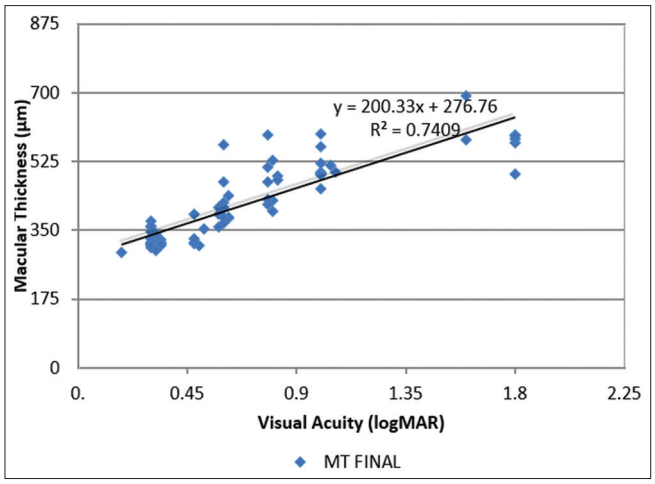

Figure 1: Showing correlation between macular thickness and visual acuity

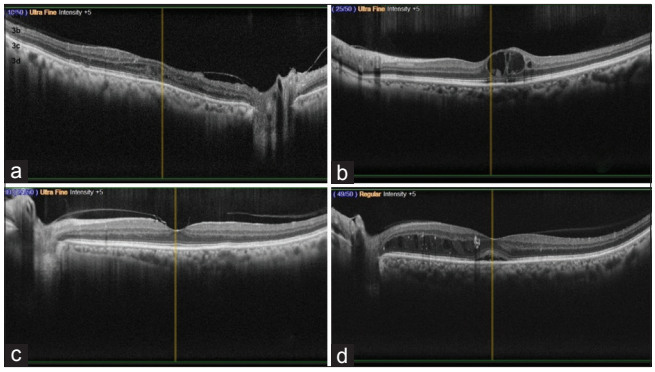

Figure 2: Optical coherence tomography scans showing (a) diffuse retinal thickness, (b) cystoid macular edema, (c) posterior hyaloid traction, and (d) serous retinal detachment

± 99.94106 and mean total macular volume of the study was 10.8113 ± 2.13107.

In this study, four morphological patterns of DME were observed on OCT, that is, DRT, CME, PHT, and SRD. In our study, 31 patients (43.1%) had DRT, 21 patients (29.2%) had CME, 13 (18.1%) patients had PHT, and 7 (9.7%) patients had SRD on OCT. The mean macular thickness was significantly high in patients with CME (33.14 ± 65.00) when compared with macular thickness in DRT (323.06 ± 18.31), PHT (414.46±55.05), and SRD (449.71±49.83). Similarly, Acan *et al.*[10] also observed the highest mean CMT in CME pattern (593.7 ± 165.3) and the lowest in DRT (313.6 ± 94.7). On the contrast, Kim *et al.*[7] showed highest mean CMT in patients with PHT and TRD. Mean total macular volume was highest in patients with cystoid pattern (13.12 ± 2.133) and least in DRT pattern (9.42 ± 0.69). The difference was highly significant ($P < 0.001$).

Similar to our observations, DRT was the predominant morphological pattern reported by Kim *et al.*[7] (39.5%), Acan *et al.*[10] (36.8%), and Luxmi *et al.*[16] (59.8%). It was followed by CME in 29.2% in our study, 21.8% by Luxmi *et al.*,[16] and 24.7% by Qureshi *et al.*,[18] whereas Otani *et al.*[14] reported DRT in 88%, CME in 47%, and SRD in 15% of all his patients. Figures were apparently higher as compared to our study as they had reported prevalence of morphology inclusive of all combination of patterns of maculopathy, whereas we considered only the worst grade of maculopathy.

Predominant morphological pattern observed in males was DRT (34.7%), while in females was CME (20.8%). Out of 31 patients of DRT, 25 (80.6%) were male and out of 21 patients with CME, 15 (71.4%) were female. Acan *et al.*[10] showed no significant difference between the DME patterns in respect of gender, whereas Luxmi *et al.*[16] reported that 42.3% of male patients had DRT pattern, while 100% female diabetics had CME.

The mean age of patients with SRD pattern was 70.71 ± 4.82 and that of DRT pattern was 48.55 ± 2.7. The difference was statistically significant ($P < 0.001$). No significant association of age was found by Luxmi *et al.*[16] and Acan *et al.*[10]

Mean duration of diabetes in patients with DME was longest (20.86±3.58 years) in SRD group and shortest (4.52±2.77 years) in DRT Group. In a study done by Luxmi *et al.*,[16] duration of diabetes in 47.4% of patients with CME and 31.3% of patients with SRD was as long as 20–40 years, whereas no significant association was observed by Acan *et al.*[10] Mean HbA1c in patients with SRD was 11.53 ± 1.35. It was significantly higher than in DRT (7.19 ± 0.76), CME (8.56 ± 1.04), and PHT (10.09 ± 1.76). This finding was consistent with the results recorded by Acan *et al.*[10] Both WESDR and DCCT have documented the affect of HbA1c level on the occurrence and progression of DME.[19] There are also studies in the literature that have postulated that with decrease of HbA1c, rate of DME, and subsequent micro vascular complications decrease.[20,21]

Total cholesterol level was significantly deranged in patients with CME (270.92 ± 52.04) compared to other morphological types of DME. Almost all patients had abnormal serum triglycerides levels with highest mean level of 256.58 ± 83.44 in patients with CME ($P = 0.000$). It was similar to the results by Luxmi *et al.*,[13] Zendar *et al.*,[22] and Gupta *et al.*[23] who concluded that majority of their patients with CME showed hypertriglyceridemia.

Similar to the results seen in studies by Zendar *et al.*[22] and Gupta *et al.*,[23] the mean serum LDL level in our study was within the normal range in patients with DRT and was deranged in non-DRT groups with significant high

levels in CME (P = 0.012). Studies in the literature have shown serum creatinine as an independent risk factor for maculopathy.[22,24] Aiello *et al.*[24] even confirmed reversal of macular edema after dialysis in some patients. We observed significant rise in serum creatinine (1.3 6 ± 0.49) and blood urea level (59.85 ± 31.37) in patients with SRD (P = 0.000). Likewise, Acan *et al.*[10] and Ghosh *et al.*[25] also found higher serum creatinine level in the SRD than in other patterns. Increased serum levels of urea and creatinine are significant markers for disruption of retinal photoreceptor external limiting membrane and inner segment ellipsoid zone in diabetics.[26] However, a study done by Ghosh *et al.*[25] did not show any correlation of blood urea with any type of DME.

About 34.7% of the patients in our study group showed albuminuria out of which 8.3% had macroalbuminura and 26.4% had microalbuminuria. Macroalbuminuria was significantly associated with SRD (83.3%), whereas microalbuminuria was significantly associated with CME (63.2%) P = 0.000. Study by Koo *et al.*[27] showed that serous type was more frequently seen in patients with albuminuria.

In our study, hypertension was not found to be significantly correlated with patterns of DME with (P = 0.265), while smokers, alcoholics, insulin users, and obese patients showed statistically higher prevalence of CME as compared to DRT, PHT, or SRD. Luxmi *et al.*[16] showed a positive correlation of insulin with CME (P = 0.003), whereas Acan *et al.*[10] showed no such correlation. In this study, only 22.2% patients were smokers and among them, the majority (75%) belonged to CME group P = 0.000. It was similar to the observations by Luxmi *et al.*,[16] (73.7%), but Romero *et al.*[28] showed no significant association between smoking and DME. Only 18% of the patients were alcoholic and majority (92.3%) of them showed CME pattern P = 0.000. None of the patient with PHT or SRD gave history of alcohol consumption. Acan *et al.*,[29] also in their study in Turkey, confirmed that DME was significantly associated with alcohol consumption.

Visual acuity was worst (1.21 ± 0.40 LogMAR) affected in CME pattern and least in DRT group (0.34 ± 0.074 LogMAR). The difference was statistically significant (P = 0.000) P = 0.000. Studies done by Yamamoto *et al.*,[30] Acan *et al.*,[10] and Ahmadpour-Baghdadabad *et al.*[31] also recorded visual acuity to be worse in CME as compared to other groups. In contrast to ours, studies done by Alkuraya *et al.*[12] and Yassin *et al.*[13] reported the worst visual acuity to be in vitreoretinal traction type and SRD, respectively.

CONCLUSION

Our study concludes that the most common pattern in 14.4% of patients with DME is DRT (43.1%) followed by CME (29.2%), PHT (18.1%), and SRD (9.7%). The mean age of patients with DRT pattern was minimum (48.55 ± 2.7) and maximum in SRD pattern (70.71 ± 4.82). Mean duration of diabetes was longest in SRD pattern (20.86 ± 3.58) and shortest in DRT pattern (4.52 ± 2.77). Male gender was correlated with higher prevalence of DRT and female gender with CME. CME is associated with use of insulin, smoking, alcohol consumption, and deranged lipid profile. Patients with deranged renal profiles and higher HbA1c level had significantly higher prevalence of SRD. Hypertension did not show any significant association with the study groups. A higher foveal thickness and increased total macular volume were associated with significant deterioration of visual acuity.

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