Correlating the patterns of diabetic macular edema, optical coherence tomography biomarkers and grade of diabetic retinopathy with stage of renal disease

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Abstract

Purpose To correlate optical coherence tomography (OCT)-based morphological patterns of diabetic macular edema (DME), biomarkers and grade of diabetic retinopathy (DR) in patients with various stages of chronic kidney disease (CKD) secondary to diabetes.

Design Multicentric retrospective cross-sectional study was conducted at seven centers across India.

Methods Data from medical records of patients with DME and CKD were entered in a common excel sheet across all seven centers. Staging of CKD was based on estimated glomerular filtration rate (eGFR).

Results The most common morphological pattern of DME was cystoid pattern (42%) followed by the mixed pattern (31%). The proportion of different morphological patterns did not significantly vary across various CKD stages ($p=0.836$). The presence of external limiting membrane-ellipsoid zone (ELM-EZ) defects ($p<0.001$) and foveal sub-field thickness ($p=0.024$) showed a direct correlation with the...
stage of CKD which was statistically significant. The presence of hyperreflective dots (HRD) and disorganization of inner retinal layers (DRIL) showed no significant correlation with the stage of CKD. Sight threatening DR was found to increase from 70% in CKD stage 3 to 82% in stages 4 and 5 of CKD, and this was statistically significant ($p = 0.03$).

**Conclusion**  Cystoid morphological pattern followed by mixed type was the most common pattern of DME on OCT found in patients suffering from stage 3 to 5 of CKD. However, the morphological patterns of DME did not significantly vary across various CKD stages. ELM-EZ defects may be considered as an important OCT biomarker for advanced stage of CKD.

**Keywords**  Morphological pattern · DME · CKD · eGFR · OCT biomarkers

**Introduction**

Diabetic retinopathy (DR) is one of the leading causes of sight threatening disease in the world. It is estimated that by the year 2030 there would be 366 million diabetics [1]. DR is responsible for 4.8% of the 37 million cases of blindness throughout the world. The most common cause of vision loss in patients with DR is diabetic macular edema (DME) found in 11.5%, followed by macular ischemia or complications of neovascularization like vitreous hemorrhage or retinal detachment [2, 3].

An increase in the number of people suffering from diabetes would see a parallel increase in the diabetes associated microvascular complications like retinopathy, nephropathy and neuropathy. These microvascular complications are linked to the duration of diabetes mellitus (DM), poor glycemic control and systolic hypertension [3]. The presence of DR is a risk factor for development of overt nephropathy, whereas overt nephropathy is a significant factor for sight threatening DR [4]. The prevalence of overt diabetic nephropathy is 2.2% [5]. The presence of concomitant nephropathy with retinopathy can lead to early progression of the DME, and albuminuria is said to correlate with DME [6]. Penno et al. and Grunwald et al. have shown the association of estimated glomerular filtration rate (eGFR) with DR in type-2 diabetes and demonstrated an independent inverse correlation between eGFR and DR [7, 8]. Moderate to severe CKD is estimated to be found in 15–23% of patients with diabetes [9]. Also, the features of diabetic nephropathy occur at a later stage as compared to retinopathy; hence, a patient with DR needs to be closely monitored.

Optical coherence tomography (OCT) plays an important role in identifying various morphological patterns and biomarkers in patients with DME [10, 11]. The morphological patterns of DME described are diffuse, cystoid, serous retinal detachment (SRD), mixed type and vitreomacular traction (VMT) [11, 12]. Various biomarkers such as disorganization of the inner retinal layers (DRIL), hyperreflective dots (HRD) and defects of the external limiting membrane-ellipsoid zone (ELM-EZ) have been described on OCT in eyes with DME [13–16].

DRIL likely represents an anatomic interruption in the visual transmission pathway. Disruption has been hypothesized to result when bipolar axons snap after their elasticity limit has been exceeded due to edema [17]. This disorganization of cells within inner retinal layers, including bipolar, amacrine or horizontal cells, possibly indicates a disruption of pathways that...
transmit visual information from the photoreceptors to the ganglion cells [13].

HRD is a clinical marker of outer blood retinal breakdown and consequent photoreceptor dysfunction. Breakdown of the blood–retinal barrier induces further thickening of the retina parenchyma and extravasation of macromolecules or macrophages. Their presence in the foveal area was found to be a negative prognostic factor for the final visual outcome [15, 16].

OCT provides high-resolution images and gives precise information of the morphological pattern and retinal thickness, thereby guiding the treatment protocols.

To date, very few studies have been conducted to determine the correlation between the morphological pattern of DME in patients with chronic kidney disease (CKD) secondary to diabetes [12]. The present study was conducted to correlate OCT-based morphological patterns of DME and biomarkers in patients with various stages of CKD secondary to diabetes.

**Methods**

It is a multicentric retrospective cross-sectional study conducted at seven centers across India. Review of the medical records was done of patients with a history of DM with deranged renal functions having DR with DME on clinical and OCT evaluation from January 01, 2019, to December 31, 2020. The study followed the declaration of Helsinki, and ethical clearance was taken from each center. A written informed consent was taken from all the patients to use the data for research purpose.

A common excel sheet was shared with all the centers, and the following data were captured from the medical records—demographic profile, duration of diabetes, level of glycosylated hemoglobin (HbA1c), duration of nephropathy, history of hypertension and renal dialysis, renal profile including serum urea, serum creatinine and eGFR. Ophthalmic examination details such as best corrected visual acuity (BCVA), grading of DR (ETDRS grading) and the presence of DME were noted [18]. The DR was further grouped into two categories for statistical analysis—non-sight threatening and sight threatening DR. Non-sight threatening DR included cases of mild to moderate non-proliferative DR (NPDR). Sight threatening DR included severe NPDR, early and high-risk proliferative DR (PDR) [19].

Patients included were treatment naive DR patients aged > 18 years with type-2 diabetes with CKD, i.e., serum urea > 40 mg/dl, serum creatinine > 1.6 mg/dl and eGFR < 60 ml/min/1.73m² (systemic condition test done within one month of the OCT performed) having good-quality OCT scans and color fundus photograph. One eye of each patient was included having higher foveal sub-field thickness.

eGFR was calculated using CKD-EPI Creatinine Equation (2009) which uses an online eGFR calculator provided by National Kidney Foundation [20]. This calculator requires serum creatinine, age, gender and race of the patient to be entered in the formulae to get the value of eGFR in ml/min/1.73 m². Patients were categorized into stages of CKD on the basis of eGFR-stage 3 moderate CKD (eGFR = 30–59 mL/min), stage 4 severe CKD (eGFR = 15–29 mL/min) and stage 5 end-stage CKD (eGFR < 15 mL/min) [21].

Patients excluded were aged less than 18 years, who had previously undergone laser photocoagulation or intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) or steroids, as it may alter the morphological pattern of DME, poor-quality color fundus images not allowing the grading of DR and poor image quality of OCT scan. A horizontal raster scan of 12 × 12 mm length was taken through the foveal center. The OCT image at baseline was reviewed for the morphological pattern of DME present and divided into the following 5 types-1. Spongiform pattern, 2. Cystoid pattern, 3. SRD, 4. VMT and 5. Mixed type (including both SRD and cystoid pattern) (Fig. 1). The biomarkers evaluated on OCT were foveal sub-field thickness, HRD, DRIL and ELM-EZ defects. The foveal sub-field thickness was measured manually at the fovea as the distance between the inner limiting membrane and the outer boundary of the retinal pigment epithelium—Bruch’s complex using caliper tool of the OCT [22].

The various patterns of DME were defined based on their unique appearance on OCT imaging (Fig. 1) [11, 23]

1. Spongiform pattern-Increased retinal thickness (defined as greater than 200 µm) with reduced intraretinal reflectivity and expanded areas of
lower reflectivity, especially in the outer retinal layers greater than 200 µm in width.

2. Cystoid pattern- 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

3. Serous retinal detachment- 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 distinguished subretinal from intraretinal fluid.

4. Vitreomacular traction- Peak-shaped detachment of the retina.

5. Mixed type- Co-existence of serous and cystoid macular edema.

Disorganization of the retinal inner layers (DRIL)

Inability to define boundaries between the ganglion cell–inner plexiform layer complex, inner nuclear layer, and outer plexiform layer could not be identified within central 1 mm of fovea [14].

Fig. 1 Five different morphological patterns of diabetic macular edema on optical coherence tomography. a Spongiform type, b cystoid type, c serous retinal detachment type, d vitreomacular tractional type and e mixed type (serous + cystoid)
Hyperreflective retinal dots (HRD)

The presence of intraretinal hyperreflective dots of size less than 30 μm, with the absence of back-shading and reflectivity similar to retinal nerve fiber layer [24].

ELM-EZ defects

Disrupted hyperreflective bands within the photoreceptor layer [19].

The above definitions of the morphological types of the diabetic macular edema and OCT biomarkers with a prototype image were shared with all the centers for training purpose. A sample of 10 random images were used to know the level of agreement between the seven OCT graders (one from each center). The intraclass coefficients estimated from the sample using a two-way random effect model and single rater unit (ICC2) were 0.926 for morphological pattern, 0.666 for HRD, 0.523 for DRIL and 0.714 for ELM-EZ defect. Since the ICC estimates were reasonably high, we had a single OCT grader assessing all images from the respective centers.

Statistical analyses were performed using R version 4.0.3. The results were expressed as mean ± SD if the variables were continuous, and as percentage, if categorical. Categorical variables were analyzed using Fisher’s exact test and continuous ones using Kruskal–Wallis test. Random forest model (multivariate analysis) was applied to assess the relative importance of the covariates in predicting the morphological pattern of DME. The covariates include age, grading of diabetic retinopathy, HBA1C level, duration of nephropathy, renal dialysis status and the stage of CKD. The random forest model ranked the covariates according to their importance in reducing impurities (measured by the Gini coefficient) in the model. P value of ≤0.05 was considered as significant.

Results

A total of 234 eyes of 234 patients with type-2 diabetes with CKD with DR and DME were included in the study. One hundred and seventy-five (75%) males and 59 (25%) female patients were enrolled. Mean duration of DM was 12 years (range 1–40 years). Treatment for DM included insulin in 101 (43%), oral hypoglycemic agents (OHA) in 110 (47%) and both OHA and insulin therapy in 23 (10%) patients. A total of 19 (8%) out of 234 (8%) of patients were on renal dialysis. 55% of patients with CKD stage 5 had HbA1c level > 10 mg% (Table 1).

Severity of DR and CKD

Sight threatening DR was found to increase from 70% in CKD stage 3–82% in stage 4 and 5 of CKD. The results were statistically significant and consistent (p=0.03) (Table 2).

Morphological patterns of DME and CKD

The most common morphological pattern of DME was cystoid pattern 42% (95% CI 36–49%) followed by mixed pattern (31% (95% CI 24–38%) and then the spongiform pattern in 16% (95% CI 11–22%). The SRD and VMT constituted only 6% (95% CI 0–12%) and 5% (5% CI 0–12%), respectively. The proportions of different morphological patterns do not significantly vary across various CKD stages (p=0.836, Fisher’s exact test) (Table 2).

On analyzing the OCT pattern of patients on renal dialysis (19 out of 234 patients), the most common type found was cystoid pattern. Although the association between the OCT pattern and renal dialysis is not statistically significant at 5% level (p=0.06, Fisher’s exact test), it is quite close to the level of significance. Statistical significance at 5% level would have been established had the sample size been a little higher (Table 3).

On correlating level of HbA1c with the morphological pattern of DME, it was found that the cystoid pattern on OCT was the most common irrespective of the level of the HbA1c. This was not statistically significant (p=0.15, Fisher’s exact test). 50% of the patients with HbA1c > 10% (poorly controlled diabetes) showed VMT (Table 3).

According to the multivariate analysis done using random forest model, the most important variable was HbA1c level (39.94), followed by age (37.80),
duration of nephropathy (29.43), grading of diabetic retinopathy (16.03), CKD stage (11.0) and renal dialysis (3.29). However, overall the model results are not significant ($p = 0.17$ permutation test, probability error 63%).

OCT biomarkers and stage of CKD

Detailed distribution of OCT biomarkers with stage of CKD is shown in Table 2. The presence of HRD increased from 68% in CKD stages 3 and 4 to 83% patients in CKD stage 5. However, this was found to be statistically not significant ($p = 0.13$). The presence of DRIL was found to have a similar distribution in all the three stages of CKD, and it ranged from 43 to 50%. The presence of ELM-EZ defects showed a direct correlation with the stage of CKD. They were present in 17 out of 27 patients (63%) in CKD stage 5 and in 30 out of 52 (58%) and 24 out of 83 patients (29%) with CKD stage 4 and stage 3, respectively. This was found to be statistically significant ($p < 0.001$). A direct correlation was found between foveal sub-field thickness and stage of CKD. Maximum mean foveal sub-field thickness of $524.6 \pm 178.8 \, \mu m$ was found in CKD stage 5 and $463.3 \pm 220 \, \mu m$ and $455.82 \pm 166.36 \, \mu m$ in CKD stages 4 and 3, respectively. This was found to be statistically significant ($p = 0.024$, Kruskal–Wallis test) (Table 2).

Discussion

Very few studies have been conducted to determine the correlation of non-ocular factors such as CKD secondary to diabetes with various morphological patterns of DME seen on OCT [12, 25, 26]. Also, the previous studies conducted were single-center studies with a relatively small sample size. None of the studies performed have demonstrated the impact of CKD on the recently described OCT biomarkers in DME and correlated them. This study bridges this gap in knowledge which may help in better management. On review of literature, several studies have used proteinuria as a marker of nephropathy and found a relation between disease severity and proteinuria [12, 26, 27]. However, an inconsistent relation has been reported between the two and therefore in our study we have used eGFR as a marker of nephropathy which is possibly a better marker for nephropathy as

| Table 1 Demographic data of study cohort |
|----------------------------------------|
| CKD                                    | Stage 3 n(%) | Stage 4 n(%) | Stage 5 n(%) | p value |
|----------------------------------------|--------------|--------------|--------------|---------|
| Sex                                    | Male 96(82)  | 47(63)       | 32(76)       | 175(75) | 0.011 |
|                                       | Female 21(18)| 28(37)       | 10(24)       | 59(25)  |       |
|                                       | Total 117    | 75           | 42           | 234     |       |
| Systemic treatment                     | Insulin 51(42)| 34(44)       | 16(43)       | 101(43) | 0.982 |
|                                       | OHA 56(47)   | 35(45)       | 19(52)       | 110(47) |       |
|                                       | Mixed (insulin and OHA) 13(11)| 8(11)       | 2(5)         | 23(10)  |       |
|                                       | Total 120    | 77           | 37           | 234     |       |
| HbA1c (%)                              |≤ 8 44(38)    | 33(44)       | 15(36)       | 92(39)  | 0.127 |
|                                       |> 8—≤ 10 25(21)| 18(24)       | 4(9)         | 47(20)  |       |
|                                       |> 10 48(41)  | 24(32)       | 23(55)       | 95(41)  |       |
|                                       | Total 117    | 75           | 42           | 234     |       |
| Renal dialysis                         | Yes 1(1)     | 1(1)         | 17(40)       | 19(8)   | <0.001 |
|                                       | No 116(99)   | 74(99)       | 25(60)       | 215(92) |       |
|                                       | Total 117    | 75           | 42           | 234     |       |

CKD chronic kidney disease, HbA1c glycated hemoglobin, mg milligram, n number, OHA oral hypoglycemic agents
ethnic variations and age of the patient are used for its determination. Also, eGFR is possibly the earliest marker for nephropathy and albuminuria is an inconsistent marker that may regress or progress [25, 28].

In our group of patients, the average duration of diabetes was 12 years or more with stage 3, 4 or 5 CKD and the proportion of different morphological patterns of DME on OCT did not significantly vary across various CKD stages. However, the most common morphological pattern found in the study cohort was cystoid pattern 42% (95% CI 36–49) followed by mixed pattern 31% (95% CI 24–38) and then the spongiform pattern in 16% (95% CI 11–22). This is in contrast to what has been reported by Koo et al. in their retrospective study on 93 Korean patients of DME with renal dysfunction [12]. They found that the serous macular edema occurred most commonly (67%) and this possibly is due to albumin and other extracellular fluid leaking into the sub-retinal space leading to serous detachment [12]. Romero et al. in a series of 112 Spanish patients of type-1 DM of which 23 patients had DR and nephropathy, found spongiform DME to be the most common pattern in 78% patients (18 out of 23) followed by cystoid pattern in 9% (2 out of 23) [26]. Ciardella et al. have reported a case of mixed type (serous and cystoid) macular edema in patients with albuminuria [29]. This shows the variability in the morphological pattern of the DME found on OCT in patients with CKD, and no single pattern can be correlated with it.

There is paucity of information in the literature regarding the correlation of sight threatening DR with stages of CKD [7, 8]. We found sight threatening DR to increase from 70% in CKD stage 3–82%.

| Table 2 Correlation of various OCT parameters with CKD staging |
|-----------------------------|-------------|-------------|-------------|-------------|
| CKD                         | Stage 3 n(%)| Stage 4 n(%)| Stage 5 n(%)| p value     |
| Morphological pattern       |             |             |             |             |
| Spongiform pattern          | 21(18)      | 12(16)      | 5(12)       | 38(16)      | 0.836       |
| Cystoid pattern             | 50(43)      | 27(36)      | 22(53)      | 99(42)      |             |
| SRD                         | 6(5)        | 6(8)        | 1(2)        | 13(6)       |             |
| VMT                         | 6(5)        | 3(4)        | 3(7)        | 12(5)       |             |
| Mixed type (cystoid and SRD)| 34(29)      | 27(36)      | 11(26)      | 72(31)      |             |
| Total                       | 117         | 75          | 42          | 234         |             |
| Grading of DR               |             |             |             |             |             |
| Non-sight threatening       | 35(30)      | 10(13)      | 10(24)      | 55(23)      | 0.03        |
| Sight threatening           | 82(70)      | 65(87)      | 32(76)      | 179(77)     |             |
| Total                       | 117         | 75          | 42          | 234         |             |
| OCT biomarkers              |             |             |             |             |             |
| HRD                         |             |             |             |             |             |
| Present                     | 79(68)      | 51(68)      | 35(83)      | 165(71)     | 0.13        |
| Absent                      | 38(32)      | 24(32)      | 7(17)       | 69(29)      |             |
| DRIL                        |             |             |             |             |             |
| Present                     | 52(44)      | 32(43)      | 21(50)      | 105(45)     | 0.73        |
| Absent                      | 65(56)      | 43(57)      | 21(50)      | 129(55)     |             |
| ELM-EZ defect*              |             |             |             |             | <0.001      |
| Present                     | 24(29)      | 30(58)      | 17(63)      | 71(44)      |             |
| Absent                      | 59(71)      | 22(42)      | 10(37)      | 91(56)      |             |
| Foveal subfield thickness (µm) (mean ± SD) | 455.82 ± 166.36 | 463.36 ± 220.7 | 524.6 ± 178.8 | 470.58 ± 188.48 | 0.024 |

*ELM–EZ defect data are available for 162 patients out of 234 patients

CKD chronic kidney disease, DR diabetic retinopathy, DRIL disorganization of the inner retinal layers, ELM–EZ external limiting membrane—ellipsoid zone, HRD hyperreflective dots, µm micrometer, n number, OCT optical coherence tomography, SD standard deviation, SRD serous retinal detachment, VMT vitreomacular traction
in CKD stages 4 and 5. This was found to be statistically significant and consistent \((p = 0.03)\). It was also noted that the percentage of sight threatening DR was significantly different across all morphological patterns. The highest percentage risk was seen with VMT (100%) followed by SRD (92%), spongiform (82%), mixed (78%) and minimal in cystoid (69%). This highlights the fact that with advancement in the stage of CKD the patient has an increased risk of loss of vision.

In our study on subgroup analysis of patients on renal dialysis (19 out of 234 patients), spongiform pattern was not found in any patient and cystoid pattern was the commonest though not found to be statistically significant. This is in contrast to what has been reported by Takamura et al. who in their series of 118 eyes of patients on hemodialysis found spongiform pattern of DME to be the most common pattern in 53% (62 out of 118 eyes) [30].

Longer duration of DM, age, hypercholesterolemia, poor glycemic control (elevated HbA1c), hypertension and the use of insulin are regarded as major risk factors for manifestation of DME [3]. In our study glycosylated hemoglobin (HbA1c) was found to be in the higher range > 10 mg% in patients with more advanced stage of CKD and on correlating level of HbA1c with the morphological pattern of DME. It was found that cystoid pattern was the most common irrespective of the level of the HbA1c. However, this was not found to be statistically significant. An observation was made that 50% of the patients with HbA1c > 10% (poorly controlled diabetes) showed VMT. This possibly could be due to the primary insult of hyperglycemia leading to the development and acceleration of advanced glycation end products (AGEs) which promotes leukostasis and cause damage to both pericytes and endothelial cells. They are also believed to promote mechanical changes in the vitreous and at the vitreous-retinal interface promoting VMT and subsequent DME [31, 32]. This highlights the fact that the patients with poorly controlled diabetes are likely to have more VMT causing a higher risk of sight threatening DR.

To the best of our knowledge, there is a lacunae in literature regarding the impact of CKD on various OCT biomarkers. In our study on correlating the OCT biomarkers with stage of CKD we found ELM-EZ defects showed a direct correlation with the stage of CKD. They were present in 17 out of 27 patients (63%) in CKD stage 5 and in 30 out of 52 (58%) and 24 out of 83 patients (29%) with CKD stage 4 and stage 3, respectively. This was found to be highly statistically significant. DRIL and HRD showed no correlation. This suggests that patients suffering from

### Table 3: Correlation of severity of DR, glycemic control and renal dialysis with morphological pattern of DME on OCT

| Morphological pattern of DME on OCT | Spongiform pattern n(%) | Cystoid pattern n(%) | SRD n(%) | VMT n(%) | Mixed type n(%) | Total n(%) | \( p \) value |
|-----------------------------------|-------------------------|----------------------|---------|----------|----------------|-----------|-------------|
| Grading of DR                     |                         |                      |         |          |                |           |             |
| Non-sight threatening             | 7 (18)                  | 31 (31)              | 1 (8)   | 0 (0)    | 16 (22)        | 55 (23)   | 0.05        |
| Sight threatening                 | 31 (82)                 | 68 (69)              | 12 (92) | 12 (100)| 56 (78)        | 179 (77)  |             |
| Total                             | 38                      | 99                   | 13      | 12       | 72             | 234       |             |
| HbA1c (%)                         |                         |                      |         |          |                |           |             |
| \( \leq 8 \)                      | 16 (42)                 | 43 (44)              | 4 (31)  | 4 (33)   | 25 (35)        | 92 (39)   | 0.15        |
| \( > 8—\leq 10 \)                 | 9 (24)                  | 15 (15)              | 7 (54)  | 2 (17)   | 14 (19)        | 47 (21)   |             |
| \( > 10 \)                        | 13 (34)                 | 41 (41)              | 2 (15)  | 6 (50)   | 33 (46)        | 95 (40)   |             |
| Total                             | 38                      | 99                   | 13      | 12       | 72             | 234       |             |
| Renal dialysis                    |                         |                      |         |          |                |           |             |
| Yes                               | 0 (0)                   | 12 (12)              | 1 (8)   | 2 (17)   | 4 (6)          | 19 (8)    | 0.06        |
| No                                | 38 (100)                | 87 (88)              | 12 (92) | 10 (83)  | 68 (94)        | 215 (92)  |             |
| Total                             | 38                      | 99                   | 13      | 12       | 72             | 234       |             |

**Notes:**
- **DME:** diabetic macular edema
- **DR:** diabetic retinopathy
- **HbA1c:** glycated hemoglobin
- **mg:** milligram
- **n:** number
- **OCT:** optical coherence tomography
- **SRD:** serous retinal detachment
- **VMT:** vitreomacular traction

\( DME \) diabetic macular edema, \( DR \) diabetic retinopathy, \( HbA1c \) glycated hemoglobin, \( mg \) milligram, \( n \) number, \( OCT \) optical coherence tomography, \( SRD \) serous retinal detachment, \( VMT \) vitreomacular traction
diabetes and end-stage CKD show more ELM-EZ defects on OCT causing poorer visual prognosis. In a patient suffering from diabetes if on evaluation of OCT one finds ELM-EZ defects, then it is important to check the renal function in such patients, if they are not aware of it.

Knudsen et al. studied DME in 20 patients with type-2 DM and found a strong correlation between increased retinal thickness on OCT and increased urinary albumin excretion rate [6]. Acan D et al. in their study of 53 patients with DME found that diffuse retinal thickness (62%) was much higher with micro- or macro-albuminuria compared to cystoid macular edema (42%) and SRD (21%). They also found that the HbA1c levels were higher in the diffuse retinal thickness group [33]. We found a direct correlation between foveal subfield thickness and stage of CKD. Maximum mean foveal sub-field thickness of 524.6±178.8 µm was found in CKD stage 5. It was noted to be 463.3±220 µm and 455.82±166.36 µm in CKD stages 4 and 3, respectively. This was found to be statistically significant.

All the previous studies conducted were single-center studies with a relatively small sample size. The present study is the first from the Indian subcontinent and the largest multicentric series till date. It is also the first study to correlate eGFR with the morphological pattern of DME, sight threatening DR and OCT biomarkers with stage of CKD. The limitations of this study are as follows: it is a retrospective study, there was no control group with no CKD for comparison, the sample size of patients on renal dialysis was small to draw conclusions, thereby requiring a further study with larger sample size and the OCT biomarkers were graded qualitatively but not quantitatively [34, 35].

Conclusion

Cystoid morphological pattern followed by mixed type was the most common pattern of DME on OCT found in patients with stages 3 to 5 of CKD. However, the morphological patterns of DME did not significantly vary across various CKD stages. The risk of sight threatening DR increases with the increase in the stage of CKD requiring an early referral to an ophthalmologist for a close monitoring of DR. Increased sub-foveal thickness and ELM-EZ defects may be considered as an OCT biomarker for advanced stage of CKD, and we urge clinicians to pay close attention to this finding on OCT in order to timely evaluate the renal parameters and refer to a nephrologist.

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Data availability The data are available for referencing if needed.

Declarations

Conflict of interest We have no conflict of interest with each other.

Ethical approval The manuscript has been read and approved by all the authors.

Consent for publications This manuscript has not been published elsewhere, and it has not been submitted simultaneously for publication elsewhere.

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