# Influence of Segmental Supply of Cilioretinal Artery on Morphology of Diabetic Macular Edema

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# Abstract

Background

The supply of Cilioretinal artery (CRA) to different layers of retina influences retinal pathologies like diabetic retinopathy. Since the supply of CRA is segmental, Our aim is to analyze the location of CRA) with non center-involving and center-involving diabetic macular edema (DME) and to evaluate the supply of CRA with segments of macular edema based on Early Treatment of Diabetic Retinopathy Study (ETDRS) scale using optical coherence tomography (OCT).

Design

Retrospective study

Methods and Materials

A retrospective study in which forty-three patients at various stages of diabetic retinopathy with the presence of CRA were identified. Presence and location of CRA was recognized using fundus fluorescein angiography. Diabetic retinopathy was graded based on ETDRS classification using OCT.

Results

Evaluation of 26 men and 17 women of various groups of diabetic retinopathy revealed unilateral CRA in 40 subjects and bilateral CRA in 3 subjects. When CRA supplied the central area, maximum retinal thickness was noted at the temporal quadrant (271.67±164.02 μm) and had noncenter-involving DME (194.87±121.06 μm), when CRA supplied the lower area, maximum retinal thickness was noted at the superior quadrant (293.64±159.36 μm) and had center-involving DME (395±285.75 μm), and when it supplied the upper area, maximum retinal thickness was noted at the nasal quadrant (293.49±176.18μm) with center-involving DME (292±192.79 μm).

Conclusion

The presence of CRA seems to alter the morphology and influences the segment involved in DME. However, further studies with larger sample size are warranted to prove this association.


# Introduction

The outer retina is supplied by choroidal circulation whereas the inner retina by retinal circulation. There are anatomical, hemodynamic, and autoregulatory differences in these circulations. The changes in retinal circulation are well characterized in diabetic retinopathy. However, the choroidal changes are less well understood. A recent study by Kim et al,[1] determined the choroidal vascular changes in diabetic patients by measuring the choroidal vascularity index (CVI). The authors hypothesized that a reduction in

the choroidal vascular component was apparently noted in patients with type-2 diabetes mellitus (DM), even when there is no evidence of diabetic retinopathy (DR).

The incidence of the cilioretinal artery (CRA) varies among many published reports. A study done by K S Mehra et al [2], reported the incidence of 6.9% in Indian population, Jain I S et al[3], reported 22.8% in Chandigarh population, Lorentzen et al [4], 26%, Lei Liu et al [5], 35% and Collier et al, 21.6%. Hence the incidence varies between 6% and 40%. Cilio retinal artery originates from ophthalmic artery and fills up during choroidal flow of fundus fluorescein angiography (FFA). The difference in the supply to different layers of retina by choroidal and retinal circulation may influence the phenotype in retinal pathologies such as diabetic retinopathy.

Recent studies have hypothesized that the vascular structures or substances from the choroid might influence diabetic maculopathy [6].Knudsen and Lervang[7] showed that in patients with diabetes, who had bilateral but asymmetric diabetic maculopathy, more severe maculopathy, which included clinically significant macular edema, was detected in the eye with a CRA. A study conducted by Landa et al [6] using a retinal function imager shows that there is an increased occurrence of diabetic macular edema (DME), if there is apresence of CRA in diabetic eyes.

However, usually, the supply of CRA is segmental. The effect of this segmental choroidal supply has not been evaluated in diabetic retinopathy. In this study, our focus was on the analysis of location of CRA with non center-involving and center-involving DME and to evaluate the supply of CRA with segments of macular edema based on Early Treatment of Diabetic Retinopathy Study (ETDRS) scale using optical coherence tomography (OCT).

## Subjects And Methods

Fundus fluorescein angiography database were segregated to identify people with diabetes and CRA at three tertiary care centers in south India. On screening database from 2015 to 2017, a total of 43 (26 men and 17 women) patients were identified at various stages of diabetic retinopathy with presence of CRA. All the patients in the study group had adult-onset diabetes mellitus with mild-to-severe non proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). Patients with neovascularization of the disc (NVD) and small fine cilioretinal artery at the disc margin on angiogram were excluded.

# Clinical Assessment

The demographic details and medical history including duration of diabetes-associated systemic hypertension were noted. The treatment received, including LASER and intravitreal injections and visual acuity, was noted. Fundus photos were graded for the presence of diabetic retinopathy, and diabetic retinopathy was graded based on ETDRS classification.

FFA-proven CRA side and prominent regions of the macula (upper, central, and lower) being supplied by it were noted. OCT findings were entered carefully as center-involving DME, non center-involving DME, no DME, presence of epiretinal membrane and/or taut posterior hyaloid membrane causing traction on macula and thinning suggestive of atrophy. Possible presence of CRA in the other eye was also noted. The study was approved by the Institutional Review Board (Ethics committee), Vision Research Foundation and written consent was obtained from the subjects as per the Declaration of Helsinki.

# Grading of DME

The grading of DME was done as follows:[8]

# Center-involving DME

On clinical examination, definite retinal thickening due to DME involving the center of the macula. The spectral-domain optical coherence tomography (SD-OCT) showed loss of foveal contour, cystic space involving center of fovea, and neurosensory detachment involving the center of fovea. Central subfield thickness on OCT > 290 μm for women, > 305 μm for men was observed on SD-OCT (Cirrus; Zeiss).

# Non center-involving DME

Definite retinal thickening due to DME within 3000 μm of the center of the macula but not involving the center of the macula. The SD-OCT showed cystic spaces and or retinal thickening in non central macular subfields.

# No DME

Normal central subfield thickness on OCT 209 ± 18 μm in men and 194 ± 23 μm in women.
Mean Retinal thickness according to Early-Treatment Diabetic Retinopathy Study (ETDRS) protocol [9]:

Central subfield thickness – 245.42 ± 20.42, Inner ring (Nasal – 319.7 ± 15.04, Temporal – 305.99 ± 15.61, Superior – 320.27 ± 14.44, Inferior – 316.87 ± 15.93), Outer ring (Nasal – 293.99 ± 15.16, Temporal – 260.18 ± 14.24, Superior – 276.77 ± 12.76, Inferior – 267.44 ± 13.54).

Clinically significant macular edema is considered if the retinal thickening or hard exudates are observed within 500 ± 50 μm of the center of the foveal avascular zone or zones of retinal thickening 1 disc area or larger, any part of which was within 1 disc diameter of the center of the macula [10].

# Statistical Analysis

For statistical analysis of groups and subgroups, an independent sample t-test was used. Chi-square test was used to find the association between the areas of supply of CRA with grading of DME. It was also used to compare clinically significant macular edema in eyes with and without a CRA. Mean thickness at the area of supply and central foveal thickness were presented along with SDs as mean ± SD. Binary logistic regression was used to find the relationship between center- and non center-involving DME with area of supply of CRA.

# Results

Fundus fluorescein angiography evaluation of these 43 subjects with diabetic revealed a unilateral CRA in 40 subjects and bilateral in 3 subjects. Of these 43 eyes of subjects with diabetic, 5 (11.36%) had mild NPDR, 20 (45.45%) had moderate NPDR, 12 (29.54%) had severe NPDR, and 6 (13.63%) were diagnosed to have PDR. These patients were further classified as having center-involving DME (37.20%), non center-involving DME (37.20%), and no presence of DME (25.58%) ($p = 0.83$).

(Table 1) shows the patients characteristics according to the status of macular edema in the study group. Among men, the distribution values of center-involving DME, non center-involving DME, and no DME are 68.75%, 75%, and 27.27% ($p = 0.05$). Likewise, among women the distribution values of center-involving DME, non center-involving DME, and no DME are 31.25%, 25%, and 72.72% ($p = 0.03$). No statistical significant difference was observed for age, duration of diabetes, and stages of diabetic retinopathy among the groups.

Table 1

Patients characteristics according to the status of macular edema in the study group

| DEMOGRAPHIC AND CLINICAL FINDINGS | Center involving DME* N = 16 | Non center involving DME* N = 16 | No DME* N = 11 | P Value |
|---|---|---|---|---|
| Age (Mean in years ± SD) | 59.93 ± 8.04 | 54.18 ± 7.44 | 60.08 ± 7.22 | 0.34 |
| Duration of diabetes (Mean in years ± SD) | 13.75 ± 8.32 | 11.37 ± 6.11 | 9.22 ± 1.85 | 0.1 |
| Gender N (%) | | | | |
| Male | 11 (68.75%) | 12 (75%) | 3 (27.27%) | 0.05 |
| Female | 5 (31.25%) | 4 (25%) | 8 (72.72%) | 0.03 |
| DR stage N (%) | | | | |
| Mild NPDR† | 2 (12.5%) | 1 (6.25%) | 2 (18.18%) | 0.83 |
| Moderate NPDR† | 7 (43.75%) | 10 (62.5%) | 3 (27.27%) | |
| Severe NPDR† | 4 (25%) | 4 (25%) | 4 (36.36%) | |
| PDR‡ | 3 (18.75%) | 1 (6.25%) | 2 (18.18%) | |
| *DME- Diabetic macular edema,† NPDR – Non proliferative diabetic retinopathy, ‡PDR – Proliferative diabetic retinopathy | | | | |

(Table 2) shows relationship of DME with area of supply by CRA. The subjects with center-involving DME had upper, 31.25%; central, 37.5%; and lower, 31.25% area of supply by CRA. The subjects with non center-involving DME had upper, 12.5%; central, 50%; and lower, 37.50% area of supply by CRA. The subjects with no DME had upper, 9.09%; central, 56.54%; and lower, 36.36% area of supply by CRA.

Table 2
Relationship of diabetic macular edema and area of supply by cilioretinal artery

| Area of Supply by CRA* | Upper | Central | Lower |
|---|---|---|---|
| Center involving DME† | 5 (31.25%) | 6 (37.5%) | 5 (31.25%) |
| Non center involving DME† | 2 (12.5%) | 8 (50%) | 6 (37.5%) |
| No DME† | 1 (9.09%) | 6 (56.54%) | 4 (36.36%) |
| P Value | 0.25 | 0.10 | 0.36 |
| *CRA – Cilioretinal artery, †DME – Diabetic macular edema | | | |

Table 3 shows the distribution of DME with the presence and absence of CRA. The distribution of center-involving DME in the presence of CRA is 37.2% and in the absence of CRA is 44.2%. The distribution of non center-involving DME in the presence of CRA is 39.5% and in the absence of CRA is 20.9%, and the distribution of no DME in the presence of CRA is 18.6% and in the absence of CRA is 25.5%. The presence of a CRA was observed as an important factor when the overall rates of macular edema in these eyes were compared to those of macular edema in eyes without the presence of CRA (p = 0.062).

Table 3
Distribution of diabetic macular edema with presence and absence of cilioretinal artery

| CRA Status* | Centre Involving DME† | Non-Centre involving DME | No DME |
|---|---|---|---|
| CRA Present | 37.2% | 39.5% | 18.6% |
| CRA Absent | 44.2% | 20.9% | 25.5% |
| *CRA – Cilioretinal artery, †DME – Diabetic macular edema | | | |

Table 4 shows the relationship between area of supply of CRA and area of retinal thickness. When CRA supplies the central area, the maximum retinal thickness was noted at the temporal quadrant (332.68 ± 89.95) and has non center-involving DME (194.87±121.06 mm), When CRA supplies the lower area, the maximum retinal thickness was noted at the superior quadrant (342.42 ± 88.92) and has center-involving DME (395±285.75 mm) and with CRA supply in the upper area, the maximum retinal thickness was noted at the nasal quadrant (328.44 ± 129.82) with center-involving DME (292±192.79 mm).

Table 4

Relationship between area of supply of cilioretinal artery and area of retinal thickness.

| Area of supply of CRA | Superior | Temporal | Inferior | Nasal | At fovea | P value |
|---|---|---|---|---|---|---|
| Centre | 324.34 ± 58.83 | 332.68 ± 89.95 | 320.84 ± 83.26 | 328.42 ± 77.57 | 306.10 ± 120.33 | 0.9077 |
| Upper | 293.5 ± 132.15 | 308.69 ± 160.56 | 325.13 ± 129.40 | 328.44 ± 129.82 | 317.38 ± 152.69 | 0.9818 |
| Lower | 342.42 ± 88.92 | 332.04 ± 101.38 | 319.08 ± 112.80 | 336.62 ± 127.90 | 318.69 ± 164.81 | 0.9827 |

# Discussion

In this study, we evaluated the effect of presence of CRA on the diabetic maculopathy changes in eyes compared to the changes that result in its absence. It was found that the patients with CRA had more non center-involving DME compared to center-involving DME, whereas those without CRA had more center-involving DME compared to non center-involving DME. However, this difference was not statistically significant. We also observed that if the CRA supplied the central areas, the maximum retinal thickness was noted in the non central area (temporally). It was also found that the CRA alters the morphology of macular edema. Probably, its presence protects the area supplied by it from developing macular edema. This is in contrast to the findings in the study by Landa et al[6] who reported higher rates of DME in such eyes. However, the authors did not classify the edema as center or non center involving. As the histological structure of a CRA is similar to the branches of the central retinal artery, it is assumed that it undergoes similar levels of hypoxic damage, or even more due to the absence of “auto regulatory” features, which are a hallmark of the retinal circulation.[11] However, the CRA has a high flow velocity, which may compensate for reduction of flow due to the structural changes in choroid due to diabetes.

Recently, Ebraheem et al [12] have reported that the presence of a CRA result in decreased levels of sub retinal fluid (SRF) in treatment-naive nAMD patients compared to controls who lacked a CRA. The authors concluded that CRA alters the hemodynamic of blood flow by diverting blood from the choroid to the inner retinal circulation, resulting in more chances of CME and probably a decreased chance of SRF. Probably through a similar mechanism, the distribution of DME is altered in patients with CRA.

The strength of the study was that only FFA-proven CRA were included in the study. However, this reduced the sample size in each group, as the individuals with clinical suspicious of CRA with no FFA were excluded. The systemic factors such as glycemic control, serum lipids, and blood pressure were not considered in the analysis as data for these were not available for all patients. In some cases non-central and no DME cases can progress into central involving DME, and requires longitudinal analysis of the patients which is beyond the scope of this study because of its retrospective nature. Future longitudinal studies are required to fully understand the progression.

In summary, the presence of CRA seems to alter the morphology of DME. The segmental distribution of CRA also influences the segment involved in DME. However, further studies with larger sample size are warranted to prove this association.

# Declarations

### Ethics approval and consent to participate

The study was approved by the Institutional Review Board (Ethics committee), Vision Research Foundation and written consent was obtained from the subjects as per the Declaration of Helsinki.

### Consent for publication

Not applicable

### Availability of data and materials

The datasets generated during and/or analysed during the current study are not publicly available, as it is against the organization/hospital policy. But are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests


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### Authors Contributions

R.R[1], R.K, N.S., contributed in conception and design of the study. R.K., wrote the main manuscript text and prepared all the tables. R.K. and R.R[1]. assisted with statistical analyses. R.R[1], drafted the work and substantively revised it. M.S., R.R., J.C., N.S., helped in acquisition of the data. All authors reviewed the manuscript.

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