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Study of changes in choroidal thickness with severity of diabetic retinopathy and diabetic macular edema in type 2 diabetic patients

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ABSTRACT

Introduction: Diabetic retinopathy (DR) is one of the long-term microvascular complications of Diabetes mellitus. Chronic hyperglycemia cause microvascular abnormalities to both retina and choroid. Optical coherence tomography (OCT) is a non-invasive fundus imaging modality, which plays a vital role in revealing the pathogenesis and development of retinal–choroidal diseases.

Materials and Methods: This prospective observational study included 128 eyes of 64 subjects diagnosed with type 2 diabetes and out of 128 eyes, 113 (88%) eyes were found to have DR. Collected data included age, gender, duration of diabetes, glycemic control, comprehensive ocular examination, fundus photography, and CT measurement on OCT.

Results: Mean age in the study group was 53.71 ± 9.37 years (45–70 years). Out of 113 eyes, 19 (17%) eyes were diagnosed as mild NPDR, 21 (19%) eyes had moderate NPDR, 36 (31%) eyes had severe NPDR and 37 (33%) eyes had PDR. The average SFCT in MILD NPDR was 310 ± 14.70 μm at 95% CI (1.86), MODERATE NPDR was 316 ± 17.97 μm at 95% CI (2.70), SEVERE NPDR was 326.02 ± 14.05 μm at 95% CI (4.59) and PDR was 298.55 ± 18.75μm at 95% CI. (1.41). The presence of DME significantly affects average SFCT. It was observed that choroidal thickness tends to increase as the severity DR with DME progress.

Conclusions: The average SFCT was thicker in patients with increase in severity of DR, and then SFCT decreased in patients with PDR. As the severity of NPDR increased from mild to moderate to severe NPDR, there was increase in sub foveal choroidal thickness. ($p<0.05$). PDR showed decrease in sub foveal choroidal thickness in comparison to NPDR which is highly statistically significant. $p=0.01$ ($p<0.05$). The presence of DME significantly affects average SFCT ($p<0.05$). It was observed that choroidal thickness tends to increase as the severity DR with DME progress. Thus, Choroidal thickness measurement can help in assessment of DR pathogenesis.

1. Introduction

Diabetes Mellitus (DM) has prolonged microvascular effects like diabetic retinopathy (DR), which is an important cause of vision loss in people between the age of 25 and 74 years, particularly in nations like the United States.The spread of the western way of lifestyle and population ageing have made DR a global public health concern and financial burden. Due to an increase in life expectancy and better blood sugar management, the prevalence of DM is rising globally.[1]

About 33% of the worldwide patients who are diabetic are estimated to have diabetic retinopathy where 642 million individuals are expected to face diabetes mellitus (DM) by 2040. Also, it has been noted that there is a direct positive relation between the prevalence of Diabetic Retinopathy and

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the duration of Diabetes.[2]

Chronic hyperglycemia in diabetic patients results in molecular and biochemical pathways like rise in advanced glycation end products, inflammatory oxidative stress and protein kinase C pathways activation which leads to endothelial damage and pericyte loss, which basically affects retina and choroid layers of eyes. Ischemic retinal tissue produces VEGF and retinal edema may be developed due to serum leakage because of endothelial damage.[3]

The layer between the retina and the sclera is the choroid which is a vascular layer and has a pigmented stroma. Retinal pigment epithelium, photoreceptors and the outer retina all receive their blood supply from the choroid vasculature. Increased vascular dilations, vascular tortuosity, microaneurysms, nonperfusion areas, vascular outpouchings, vascular narrowing, and choroidal neovascularization are some of the vascular changes in the choroid secondary to diabetes mellitus which are similar to vascular changes of retinal. The pathophysiology of Diabetic Choroidopathy can be derived easily by the changes seen in choroidal vasculature which also compromises the blood-retina barrier.[4]

Choroidal thickness (CT) is used to detect any abnormalities of vascular choroid and ocular diseases associated with it.[5] Choroidal thickness is the important index for measurement of changes in the choroidal vasculature and quantification of different pathological changes.[6]

Optical Coherence Tomography (OCT) is a non-invasive modality for fundus imaging which plays a crucial part in the assessment of retinal-choroidal diseases and their pathogenesis improving clinical diagnosis and research.[7]

Improvements and advancements in OCT technology has improved analysis of choroid structure and its thickness and increased visualization because of penetration of light, deeper into several layers of tissues of the eye due to swept-source OCT and enhanced-depth imaging OCT.[8]

OCT angiography has led to a gradual shift to vascular imaging from structural imaging and has provided the tool for analyzing vasculature and ocular structure quantitatively, primarily the choroidal thickness.[9]

2. Aims and Objective

1. To study the impact and relationship of structural changes in choroid with the severity of Diabetic Retinopathy with and without macular edema.
2. To measure choroidal thickness in type 2 diabetic patients with different stages of diabetic retinopathy (DR) and DME using optical coherence tomography (OCT).

3. Materials and Methods

This is a prospective observational study conducted from MAY 2021 to JULY 2022 consisted of 64 patients diagnosed with type 2 diabetes mellitus in the age group 45 – 70 years both male and female, visiting out-patient department of ophthalmology at BRD Medical College, Gorakhpur, Uttar Pradesh. Type II diabetes mellitus patients with age less than 45 years and more than 70 years of age, any history of ocular treatment or any associated ocular diseases or media opacity causing visual impairment, immunocompromised patients or patients on immuno-suppressive drugs, and unwilling patient were excluded.

After obtaining informed and written consent, data regarding profile of patients, his/ her medical history, symptoms, duration of diabetes and treatment history was recorded in pre-designed and pre-test proforma. After counselling of patient, patient underwent for visual acuity assessment by Snellen's chart, intra ocular pressure (IOP) measurement, slit lamp examination for anterior segment evaluation, direct and indirect ophthalmoscopy for fundus examination, and OCT for choroidal thickness measurement. All subjects underwent blood examination for fasting blood sugar levels, 2-hour postprandial blood sugar, and percentage of HbA1c and urine routine and microscopy.

On fundus examination, eyes were classified into stages of Diabetic Retinopathy as per the classification guidelines of Early Treatment Diabetic Retinopathy Study (ETDRS).[10]

ICMR (Indian Council of Medical Research) guidelines were used for documentation of status of Diabetes, defined a good control of diabetes when fasting plasma glucose when fasting plasma glucose level was >126 mg/dl, 2-hour postprandial glucose >200 mg/dl, random blood glucose >200 mg/dl and HbA1c >6.5%.[11]

Visual impairment was determined based on International Classification of Disease 10^{th} edition, defined as visual impairment when best corrected visual acuity (BCVA) was <6/18, low vision was defined as a BCVA <6/18 but not less than 3/60. Blindness was considered when BCVA was <3/60.[12]

3.1. Choroidal thickness (CT) measurement

In this study, Topcon 3^{rd} generation SD OCT was used to measure choroidal thickness at SUB FOVEAL REGION using manual method in all stages of diabetic retinopathy. High precision software calipers were used to measure the vertical distance manually between the chorio-scleral interface and the posterior edge of the hyper-reflective RPE layer.

3.2. Statistical analysis

Demographic and clinical characteristics were represented by frequencies and percentage. The mean ± standard

deviation is used to express the data. ANOVA and paired t tests were used to analyze the data. p-value <0.05 was considered statistically significant.

4. Results

This study enrolled 64 eligible and consented patients, with total 128 eyes examined for diabetic retinopathy on fundoscopic examination, 113 eyes were found to have different stages of DR according to ETDRS chart. OCT was done to measure sub foveal choroidal thickness in each DR patients by manual method (gold standard method).

The age distribution of patients studied range from 45-70 years with majority patients in age category of 45 – 55 years, with the average age of 53.71 years. Out of 64, 45 patients (70%) were male and 19 (30%) were female. Out of 64, 49 patients had bilateral involvement of eyes and 15 patients had unilateral involvement of eyes. Therefore, out of 128 eyes of 64 patients, 113 eyes were included in this study diagnosed with any stage of DR. Out of 113 eyes of 64 patients diagnosed with DR, maximum eyes (47.79%) had BCVA in low vision category.

Out of 113 eyes, 37 eyes (33%) with PDR (maximum), 36 eyes (31%) with severe NPDR, 21 eyes (19%) with moderate NPDR and 19 eyes(17%) with mild NPDR were detected.

Mean SFCT increases with severity of NPDR from mild (310.00 ± 14.70μm) to moderate (316.94 ± 17.97μm) to severe (326.02 ± 14.05μm) NPDR and decreases in (298.55 ± 18.75μm) PDR. Mean SFCT is more in DR with DME than DR without DME in all stages of DR. The mean SFCT in DR was found to be 312.5 ± 14.79 μm (p=0.03). The mean SFCT in DME positive patient was found to be 328.75 ± 11.5 μm (p=0.01).

Mean SFCT progressively increased with increase in duration of diabetes and was found to be maximum in patients with diabetes duration for 11-15 years which was statistically significant.

This study demonstrated that as the severity of NPDR increased from mild to moderate to severe NPDR, there was increase in SFCT (p<0.05) and PDR showed decrease in SFCT in comparison to NPDR which is highly statistically significant. (p<0.05). Sub foveal choroidal thickness in diabetic retinopathy with diabetic macular edema was found to be significantly more than DR without (p<0.05).

Table 1: Distribution of patients according to age

Age group (years)	No. of patients (n=64)	Percentage
45-55	43	67.18
56-65	15	23.43
65-75	06	9.40

Table 2: Distribution of patient on basis years of life spent with diabetes mellitus

Duration of diabetes (in years)	No. of patients (n=64)	Percentage
<5 years	12	18.75
5-10 years	35	54.69
11-15 years	14	21.88
> 15 years	3	00.05

Table 3: Distribution of stages of diabetic retinopathy

Stages of DR	No. of eyes (113)	DME Present	DME Absent
Mild NPDR	19	6	13
Moderate NPDR	21	6	15
Severe NPDR	36	20	16
PDR	37	8	29

Table 4: Choroidal thickness in DR with DME v/s DR without DME

DR	SFCT in DR with DME	SFCT INDR without DME
Mild NPDR	319.58 ± 17.15	310.00 ± 14.70
Moderate NPDR	322.20 ± 16.00	316.94 ± 17.97
Severe NPDR	335.25 ± 7.63	326.02 ± 14.05
PDR	339.00 ± 6.36	298.55 ± 18.75

5. Discussion

Diabetic retinopathy is a disease of concern and need to be diagnosed and treated as early as possible to improve quality of life and decrease prevalence and burden of disease. Choroidal parameters like choroidal thickness can help in early evaluation of choroidal and retinal pathology with advancement of technologies like OCT.

The choroid is the vascular layer that lies between retina and sclera. The five layers of choroid are Bruch's membrane (BrM), choriocapillaris (CC), Sattler layer, Haller layer, and suprachoroidal space, written anatomically from inside to outside. The choroid supplies about 90% of the ocular blood perfusion and about 70% of which is contributed by the CC layer. The layer's extensive interstices, strong blood flow, and high vascular density impact the photoreceptor cells and RPE[13] on their metabolism. Haller layer forms lobular capillaries network of large vessel calibers that parallelly run with the branch in the shape of a fan. The basis for sustaining the function of the retina and these anastomosed shunt blood balance the circulation pressure of the lobules.[14–16]

For diagnosing and monitoring the treatment of retinal diseases such as diabetic retinopathy (DR), glaucoma and age-related macular degeneration, OCT has become a standard of care.[17]

It is seen that choroidal thickness can be measured by many methods like manual method (gold standard) and automated segmentation analysis by OCT. The retina, choroid-scleral junction, and choroid layer textures were extracted using an internal image processing technique based on wavelet transform filtering. Manual analysis was found to be slower to segment the choroid than the automated software and it could eventually help us in decreasing the task time problems in a clinical setting.[18]

This study clearly shows the effect of diabetes on CT. The subjects with DR have statistically significant sub foveal choroidal thickness changes. The CT was affected by the severity of DR; eyes with PDR had thinner choroids compared to those with NPDR and many previous studies have found similar results.

The study conducted by Wang et al.[19] aims to develop the correlation between thickness of choroid (CT) and diabetic retinopathy severity (DR) and to evaluate the changes in CT in patients with diabetes and factors related to it in a large proportion of population of diabetic Chinese patients.

This study concluded increase of CT in the initial stage of DR, and further DR progression CT decreases, which is similar to our study in Indian population. Choroidal alterations even have a significant importance in the Diabetic Retinopathy pathogenesis.

Choroidal thickness alterations play a crucial role in Diabetic Retinopathy occurrence which was a result of another study conducted by Wang et al.[20] where they evaluated the associations between 2-year incidence of referable diabetic retinopathy (RDR) and choroidal thickness. One of the findings was that the development of RDR can be marked early by measuring Choroidal thickness using SS-OCT.

In a study by Endo et al.[21] the central choroidal thickness layer (CCT) in the DME+ group was found to be higher than in the DME- group with a p-value of less than 0.05. The DME- with systemic diabetic treatment group (DME-DT+) has significantly thinner total and outer CCT layer in DME+ without systemic diabetic treatment (DME+DT-) (P<0.05). In contradiction, there is no significant difference in the inner choroidal layer between the groups. In stage of DR, the control group had the inner CCT layer which was significantly thinner than severe NPDR group (P<0.05).

As per the studies carried out by Rewbury et al.[22] there was a significant increase in choroidal thickness in PDR as compared to mild NPDR group (found statistically significant with P=0.027). Moderate-to-severe non-proliferative diabetic retinopathy group did not show a statistically significant increase in SFCT as compared with the mild NPDR group (P=0.17). Patients having DR with DME were associated with a non-statistically significant increase in choroidal thickness as compared with DR without DME (P=0.13).

A statistically significant sub foveal choroidal thinning was observed in eyes with Diabetic Retinopathy when compared to subjects with Diabetes mellitus without Diabetic Retinopathy (P<0.001) and age-matched healthy eyes (P<0.011) as per the studies carried out in Sudhalkar et al.[23] Mean age in the study group was 57.0 ± 9.37 years (43–73 years). SFCT decreased with increasing severity of DR. Eyes with DR, who had undergone PRP had no significant difference in SFCT as compared to eyes that had not undergone PRP (P=0.23). The patients with PDR had significantly thinner SFCT (P=0.021) as compared to those with NPDR. The mean SFCT was not significantly different from eyes without macular edema (ME) as compared to the eyes with macular edema (P=0.196).

To evaluate sub foveal choroidal thickness (SFCT), Ambiya V et al.[24] performed a study to evaluate sub foveal SFCT change in age-matched healthy subjects as compared to diabetes and in Diabetic Retinopathy grades. The SFCT in non-proliferative Diabetic Retinopathy ($n = 64$; $SFCT = 303.25 \pm 18.59$ μm) with a p-value of less than 0.001 is significantly higher than SFCT in proliferative Diabetic Retinopathy ($n = 36$; $SFCT = 284.56 \pm 21.09$ μm). The severity of Diabetic Retinopathy was moderately in negative correlation with SFCT ($R = -0.50$; $P < 0.01$). The sub foveal choroidal thickness difference was significant only in proliferative Diabetic Retinopathy (284.56 ± 21.09 μm) with a p-value of less than 0.01, and in severe/very severe non-proliferative Diabetic Retinopathy (294.47 ± 15.65 μm; $P < 0.01$). The diabetes duration is correlated negatively with SFCT ($R = -0.41$; $P < 0.01$). These findings suggest that as duration of diabetes increases, SFCT decreases. The decrease is significant after the onset of severe DR, and is proportionate to the severity of DR.

Hamadneh et al.,[25] in his systemic review showed that as Diabetic Retinopathy worsens, there is an increase in Choroidal Thickness. Microvascular abnormalities are caused by Diabetes mellitus (DM), which might further lead to ischemia and hypoxia in adjacent retinal tissue as well as choroidal vasculature, eventually leading to increased secretion of cytokine, VEGF, that mediates fluid leakage and vascular hyper-permeability. This increased secretion of intraocular VEGF explains the increase in CT.

Many studies also suggest that in Diabetes mellitus patients with no retinopathy, in the initial stages of Diabetic Retinopathy there are changes in choroidal thickness. The decrease in the vascular layer of the choroid because of the decreasing capillary perfusion and ischemia of the choroid in the early stages explains the decrease in the choroidal thickness.

An increase in Choroidal thickness is observed as hypoxia leads to more VEGF secretion leading to neovascularization, vascular hyper-permeability, fluid leakage, increased blood flow, as the Diabetic Retinopathy progresses. These observations indicate that even without

clinical evidence of Diabetic Retinopathy, the main event in the Diabetes mellitus pathogenesis can be choroidal vasculature.

Some recent findings also show that the choroid is a more dynamic tissue than the retina and these studies also show a sudden change in plasma glucose level with a change in choroidal thickness and the extent of the severity of microangiopathy is comparable in the retina and underlying choroid.[26]

Every study has some limitation, this study did not compromise for systemic, physiologic, and local ocular variables which affect the results of Choroidal thickness and are believed to be confounders like age, length of axis, blood pressure, depth of anterior chamber, diurnal variation, refractive error, etc. Recent studies have observed choroidal thickness is affected by systemic pathological conditions, such as hypertension and renal failure.[27]

6. Conclusion

The findings conclude that the choroidal thickness is related to severity of Diabetic Retinopathy. The severity of NPDR increases SFCT proportionally while it decreases significantly in PDR and there is a significant increase in DR with diabetic macular edema. Hence, the choroid contributes significantly to the retina's blood supply; as a result, evaluating various choroid factors can aid in determining the course of DR and aid in its early diagnosis and treatment. Our results compliment the evidence that choroid changes can represent a possible pathogenesis for DR.

7. Source of Funding

None.

8. Conflict of Interest

No conflicts of interest.

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