Prevalence and Pattern of Macular Edema in Diabetes

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Abstract
Objective: Diabetic macular edema (DME) is the major cause of vision loss in patients with diabetic retinopathy (DR). The purpose of this study was to assess the prevalence of DME in pre diagnosed Type II diabetes mellitus cases, to analyze DME pattern based on Optical Coherence Tomography (OCT) images and to correlate it with glycemic control.

Methods: In cross sectional study, 200 eyes of 100 pre diagnosed type II diabetes mellitus cases were examined for DR, DME and OCT was performed to look for central macular thickness.

Result: 200 eyes were examined, 95 of them were diagnosed to have DR and 19 eyes were diagnosed to have DME. Three characteristics were found in the images of OCT in cases with DME: Diffuse retinal thickening in 9 eyes(42.4%), cystoid macular edema in7 eyes(36.8%) and serous retinal detachment in 3(15.8%). Statistical analysis showed that there was positive correlation of prevalence of DME with poor glycemic control (p<0.046), duration of diabetes (p<0.013), and severity of DR (p<0.000) but not with pattern of DME. There was statistic significance between central macular thickness and increasing grade of DME (p<0.000).

Conclusion: The prevalence of DME is 9.5% in type II diabetes mellitus cases in this study. Prevalence is correlated with DR severity, duration of diabetes, and poor glycemic control. Three patterns of DME are demonstrated with OCT images. The macular thickness is correlated to severity of DME.

Keywords: Diabetes Mellitus, Diabetic Maculopathy, Macular Edema, Pattern, Optical Coherence Tomography.

INTRODUCTION
Diabetes, one of the most common non communicable diseases, has become a global epidemic today. It is recognized as a group of heterogenous disorders with the common element of hyperglycemia and glucose intolerance, due to insulin deficiency, impaired effectiveness of insulin action or both.

Diabetic retinopathy (DR) is the leading cause of blindness and most common microvascular complication of diabetes. Nearly all patients will have some degree of retinopathy 15–20 years after diagnosis of type I diabetes.1,2 Similarly, more than 60% of type II diabetes sufferers will have evidence of DR during this period.

Retinal ischemia plays a significant role in development and progression of diabetic retinopathy.

During non-proliferative DR, the earliest visible sign of retinal damage results from abnormal permeability and/or non-perfusion of capillaries, leading to the formation of microaneurysms. Abnormal capillary permeability results in the leaking of fluid and solutes into the surrounding retinal tissue, which collects around the macula; this is referred to as macular edema (MO). PDR develops following the occlusion of retinal capillaries leading to retinal ischemia, which promotes the development of neovascularization. However, these vessels are fragile and hemorrhage easily. The risk of developing diabetic retinopathy or other microvascular complications of diabetes depends on both the duration and the severity of hyperglycemia.

Diabetic macular edema (DME) is defined as retinal thickening within 2 disc diameters of the center of the macula, results from retinal microvascular changes that compromise the blood-retinal barrier, causing leakage of plasma constituents into the surrounding retina and, consequently, retinal edema. DME left untreated, is a common cause of vision loss. DME affects central vision and can lead to decline in vision ranging from slight visual blurring to blindness. DME based on optical coherence tomography (OCT) measurements, specifically, thickness of the macula, morphology of the retina, and the presence of macular traction can be grouped into: i) Diffuse Retinal thickening, ii) Cystoid Macular edema and iii) Serous Retinal Detachment.

In this study, we aimed to evaluate the prevalence and pattern of macular edema with help of OCT in type II Diabetics and correlate it with glycemic control.

**MATERIALS AND METHODS**

**STUDY DESIGN**

The study has been conducted in accordance with the principles of the Helsinki declaration and was Approved by the local Institutional Review Board (December 4, 2015).

Cross sectional study was conducted on the Consecutive patients who presented to the outpatient clinic, and 100 Pre-diagnosed cases of Diabetes mellitus type II between 30-70 years were enrolled in the study.

Patients with any media opacity which hindered with fundus examination and patients not ready to give consent were excluded.

**OUTCOME PARAMETERS**

All subjects received comprehensive ophthalmic examinations that included best corrected visual acuity, indirect ophthalmoscopy and Slit lamp biomicroscopy. Each eye underwent macular analysis using Cirrus 500 Zeis Spectral Domain Optical Coherence Tomography.

For inclusion in study 30 – 70 years old pre diagnosed cases of diabetes mellitus type II were selected and screened for diabetic control by blood sugar fasting, post prandial blood sugar and Hb1Ac level. Detailed history of duration of diabetes and treatment taken were obtained. Any eye with condition that hindered with fundus examination was excluded from study.

Spectral domain OCT of macula was obtained using Cirrus 500 Zeis Spectral Domain OCT. 6 scans were obtained centered at macula and best scan was selected. Only good quality scan with signal strength > 7 were used for analysis. Central macular thickness was taken for evaluation. The Diffuse retinal Thickening ( DRT) was defined as sponge like macular thickening with reduced intra-retinal reflectivity. The Cystoid Macular Edema (CME) was defined as intra-retinal cystoid spaces of low reflectivity in the macular area with high reflective septa separating these spaces. The Serous Retinal Detachment (SRD) was defined as optically clear space between the neurosensory retina and the retinal pigment epithelium (RPE). Many of our patients had mixed pattern of OCT. Any presence of SRD irrespective of its association with or without any other pattern was classified as SRD variety. Any presence of cystoid
pattern irrespective of its association with or without spongiform pattern was classified as CME variety. Only those eyes with exclusive spongiform pattern were classified as DRT in our study.

Statistical analyses were performed using SPSS Statistics software (version 17.0, SPSS Inc., Chicago, IL, USA). The level of statistical significance was set at $P < 0.05$.

RESULT

100 pre diagnosed cases of diabetes mellitus type II were enrolled in study to find the prevalence of macular edema. Of 100 subjects 55 were male and 45 females. Among diagnosed macular edema cases 10 were male and 7 females. Of 200 eyes examined 19 (9.5%) eyes of 17 cases were found to have Diabetic macular edema. Eyes of cases were taken individually for all the evaluations.

Of all the eyes with macular edema 9 (47.36%) had diabetes of 11 -20 years duration and 9 eyes (47.36%) between 21-40 years duration. From data it was observed that proportion of non-retinopathy eyes was higher in eyes with duration of diabetes <10 years (82.5%) as compared to eyes with duration 10-20 years (46.2%), 21-40 years (26.3%) and >40 years (20%). A statistically significant association with presence of macular edema and duration of diabetes ($p < 0.013$) (Table 1) and severity of diabetes with duration of diabetes was observed ($p < 0.000$).

Out of 19 eyes with macular edema 9 eyes (47.4%) were classified as Diffuse retinal thickening (DRT), 7 eyes (36.8%) were classified as Cystoid macular edema (CME), and 3 (15.8%) eyes as Serous retinal detachment (SRD). Out of all the 200 eyes examined maximum were found to have no retinopathy 100(50%), those with retinopathy maximum 30 (17%) had very mild and 25 (16.5%) mild retinopathy. Minimum eyes had advanced diabetic disease 2(1%). Among eyes diagnosed with macular edema maximum had mild to moderate non-proliferative diabetic retinopathy 12 (63.2%) and none had advanced diabetic eye disease (0%). A statistically significant association of development of macular edema with severity of Diabetic retinopathy was found ($p < 0.000$) (Table 2).

Development of macular edema was found to be significantly correlated to blood sugar fasting ($p=0.042$) and Hb1Ac level ($p = 0.046$) (Table 3) but not with post prandial sugar level ($p<0.861$). Among eyes with macular edema minimum 2(10.52%) had good control i.e Hb1Ac value of $\leq 7.0\%$ while maximum eyes 10(52.6%) showed poor glycemic control i.e Hb1Ac value of $>8.5\%$. Similarly the fasting glucose was $>125\text{gm}\%$ in 15 (78.9%) eyes with macular edema. Though the pattern of macular edema was not found to be affected by diabetic control.

The treatment modality was not found to be significantly associated with presence or pattern of macular edema in our study. Maximum cases with macular edema 7 (36.8%) as well as without macular edema 98 (49%) were on oral hypoglycemic agents as compared to 74 (37%) of cases without macular edema on insulin.

Those with DRT 60.0% had central macular thickness (CMT) in range of 291-400 microns, CME 30.0% had CMT in range of 291-400, and those with SRD 50.0% had CMT of 401-500 micron. This association of CMT with pattern of macular edema was found to be significant ($p = 0.000$) (Table 4).

**TABLE 1:** Correlating Presence of Diabetic Macular Edema with Duration of Diabetes Mellitus

<table>
<thead>
<tr>
<th>DME</th>
<th>DUR</th>
<th>PRESENT</th>
<th>ABSENT</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;10</td>
<td>11-20</td>
<td>21-40</td>
<td>&gt;40</td>
</tr>
<tr>
<td>PRESENT</td>
<td>0(0%)</td>
<td>9(13.8%)</td>
<td>9(15.8%)</td>
<td>16.7%</td>
</tr>
<tr>
<td>ABSENT</td>
<td>65(100%)</td>
<td>56(86.2%)</td>
<td>48(84.2%)</td>
<td>14(93.3%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>65(100%)</td>
<td>65(100%)</td>
<td>57(100%)</td>
<td>15(100%)</td>
</tr>
</tbody>
</table>

$p < 0.013$
TABLE 2: Diabetic Retinopathy Severity (ETDRS) with Presence of Diabetic Macular Edema

<table>
<thead>
<tr>
<th>DIABETIC RETINOPATHY GRADE</th>
<th>SEVERITY</th>
<th>DME</th>
<th>PRESENT</th>
<th>ABSENT</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>NO RETINOPATHY</td>
<td></td>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>VERY MILD NPDR</td>
<td>4</td>
<td>30</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>MILD NPDR</td>
<td>8</td>
<td>25</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>MODERATE NPDR</td>
<td>4</td>
<td>9</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>SEVERE NPDR</td>
<td>0</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>MILD TO MODERATE PDR</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>HIGH RISK PDR</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>ADVANCED DIABETIC DISEASE</td>
<td>0</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>CANNOT BE EXAMINED</td>
<td>19</td>
<td>181</td>
<td>200</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3: Effect of Diabetic Control On Prevalence of Macular Edema**

<table>
<thead>
<tr>
<th>DME</th>
<th>HBA1C (gm%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRESENT</td>
<td>&lt;7</td>
<td>7-8.5</td>
</tr>
<tr>
<td></td>
<td>2 (3.4%)</td>
<td>7 (8.5%)</td>
</tr>
<tr>
<td>ABSENT</td>
<td>56 (96.6%)</td>
<td>75 (91.5%)</td>
</tr>
</tbody>
</table>

**Table 4: Pattern of macular edema in relation to Central macular thickness**

<table>
<thead>
<tr>
<th>PATTERN OF DME</th>
<th>OCT-CMT (microns)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIFFUSE RETINAL THICKENING</td>
<td>3 (60%)</td>
<td>6 (60.0%)</td>
</tr>
<tr>
<td>CYSTOID MACULAR EDEMA</td>
<td>2 (40.0%)</td>
<td>3 (30.0%)</td>
</tr>
<tr>
<td>SEROUS MACULAR DETACHMENT</td>
<td>0 (0%)</td>
<td>1 (10.0%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>5 (100.0%)</td>
<td>10 (100.0%)</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Diabetic macular edema (DME) is the major cause of vision loss in patients with diabetic retinopathy (DR). The purpose of study was to assess the prevalence of DME in pre diagnosed diabetes mellitus type II patients. Prevalence of retinopathy among diabetic patients is alarmingly high. According to a systemic review by Yau et al. (2012) which analyzed 35 studies with nearly 20,000 diabetics, the prevalence of DR was 34.6%, and DME was 6.8%. The epidemiological data form India have shown a prevalence of DR to be ranging between 22.4% - 28.9% in different studies. Within 5 years of diagnosis, only 3% of type II patients had MO, compared with 28% after 20 years duration.

For the purpose of study 200 eyes of 100 pre diagnosed cases of type II diabetes mellitus were enrolled. Majority of cases were males (55%) and aged between 50-60 years (53%). Chung et al had majority of male patients (54%) and mean age of study population as 64.9±10.8 year, almost similar to our study.

Fundus examination findings positive for retinopathy was observed in 95(47.5%) eyes. In the present study, majority of Diabetic retinopathy patients had very mild to mild non proliferative diabetic retinopathy (70.52%) followed by moderate non proliferative diabetic retinopathy (13.6%). Only 9(9.5%) cases had proliferative diabetic retinopathy. In different cross sectional studies, prevalence of different grades of retinopathy have been found to be of similar order with prevalence of lower grades of retinopathy being higher as compared to higher grades or proliferative retinopathy.

Retinopathy, a progressive disorder, assumes greater severity if remains undiagnosed and untreated hence late stages are diagnosed at advanced stages of diabetes. The higher prevalence of lower grades of diabetic retinopathy in present series is probably due to fact that in routine mild stages of diabetic retinopathy is less symptomatic and patients don’t seek medical attention.
advice so retinopathy often remains undiagnosed, however, as disease progress diagnosis is made. The prevalence of DME was found to be 9.5% which was slightly higher than previous studies conducted. This might be attributed to longer duration of diabetes and poor glycemic control in our cases. However, the pattern of macular edema was not found to be significantly related to duration of diabetes and type of treatment taken. It was observed that in general prevalence as well as severity of diabetic retinopathy increased significantly with increasing duration of diabetes. This finding correlates well with the observations of other clinical studies which had laid emphasis that early onset of diabetes poses increased risk for diabetic retinopathy.

DME was also high in patients with poor glycemic control as observed by higher levels of glycosylated hemoglobin. The CURES study has documented that for every 2% elevation of Glycosylated hemoglobin, the risk of DR increases by a factor of 1.7 %. The highest Hb1Ac levels of 7.0% are recommended by American Diabetes Association guidelines. Both WESDR and DCCT have documented the effect of Hb1Ac levels on occurrence and progression of DME.

On examining the effect of diabetic macular edema on central macular thickness a statistically significant correlation was established, with increase in central foveal thickness with increasing grade of maculopathy. SRD showed maximum cases in CMT of >401 microns while DRT showed maximum cases in CMT of range 220-290 microns. Sanchez-Toicino et al found a statistically significant increase in average foveal thickness between normal eyes and eyes of diabetics without any retinopathy. Study showed that of the type II diabetic cases who had evidence of diabetic retinopathy, 53% were treated with insulin and 28% were treated with oral hypoglycemic. Those cases who had macular edema (MO) 36.8% were on insulin. The WESDR study has shown this prevalence to be 62% and 36% in insulin treated and those treated without insulin. The effect of insulin treatment on MO prevalence has also been investigated in type II diabetics from WESDR study and MO was found to be present in 20 % of cases.

The present study provided a deep insight into relationship among type II diabetes mellitus, diabetic retinopathy and macular edema. It was observed that duration of diabetes, poor glycemic control, and higher grades of retinopathy are responsible for development of macular edema and might have a significant predictive role in prediction of severity of macular edema. As present study was limited by small sample size, a better understanding of this relationship could be gathered with the help of larger clinical trials among the Type II diabetic cases.

CONCLUSIONS

1) Prevalence of diabetic retinopathy in type II diabetic cases was 47.5 %.
2) Prevalence of diabetic macular edema in type II diabetic cases was 9.5%.
3) In present study, majority (70.52%) had very mild to mild non proliferative diabetic retinopathy.
4) Majority of patients (55%) were males and those diagnosed with DME (52.6%) were males.
5) With increasing duration of diabetes, a significant increase in occurrence of DME (p<0.013) as well as severity of diabetic retinopathy (p<0.00) was observed.
6) A significant increase in occurrence of DME was observed with poor glycemic control as observed with fasting glucose (p<0.042) and Hb1Ac (p<0.046). Though the pattern of DME was not affected by poor glycemic control.
7) DME was significantly correlated to the severity of diabetic retinopathy (p<0.000).
8) The OCT study of DME cases showed majority of eyes had diffuse retinal thickening (47.4%) and minimum had serous retinal detachment (15.8%).
9) A significant increase in central macular thickness was observed with increasing grade of macular edema (p<0.000).

The findings in present study endorsed the view that duration of diabetes, poor glycemic control, and severity of diabetic retinopathy affects the prevalence and pattern of macular edema in type II diabetic cases. The findings in present study need further substantiation.

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CONFLICT OF INTEREST: There are no conflict of interests in this study.

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