Diabetic retinopathy with or without clinically significant macular edema: The influencing factors

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Abstract

Introduction: Diabetic retinopathy is the commonest micro vascular complication in patients with diabetes and remains a leading cause of blindness in people of working age group. Objective: to determine the prevalence of clinically significant macular edema (CSME) and the influence of systemic risk factors Materials and methods: It is a hospital based comparative study conducted in 220 eyes of 110 diabetic patients. DR was graded according to International Clinical Diabetic Retinopathy Severity Scale and CSME was defined according to Early Treatment Diabetic Retinopathy Study (ETDRS) system. The patients were grouped as 1) CSME group (DR and CSME in one or both eyes) and 2) Non- CSME group(CSME in none of the eyes but with any grade of DR).Level of glycosylated hemoglobin (HbA1C), serum total cholesterol, triglyceride (TG), low density lipoprotein (LDL), high density lipoprotein (HDL) and urine for albumin were studied in both groups. Results: CSME was present in 36% of 110 patients. Poor glycemic control and high total cholesterol level showed positive association with CSME (p<0.05). LDL and TG levels were higher and HDL lower in CSME group. However, no statistical significance was found. Conclusion: The CSME is significantly associated with poorer glycemic control and elevated total cholesterol level.

Keywords: Diabetic retinopathy, Clinically Significant Macular Edema, Influencing factors

Introduction

Diabetic Retinopathy (DR)is the commonest complication of diabetes and 10% of diabetics at any time will have sight threatening retinopathy (McLeod BK et al,1988).

Macular edema is an important cause of visual impairment in patients with DR (Zander E, et al 2000).It results from the accumulation of fluid at the posterior pole of the retina and threatens visual acuity if the center of the macula is thickened (Moss SE et al,1988).The most severe form of macular edema is defined by Early Treatment for Diabetic Retinopathy Study (ETDRS) as Clinically Significant Macular Edema (CSME).

Landmark studies have shown that intensive glycemic and blood pressure control can substantially reduce the onset and progression of DR (The Diabetes Control and Complications Trial Research Group 1993; Matthews D, et al...
2004). However, the contribution of lipids to the pathogenesis of DR and CSME has been less clear (Wong TY et al., 2006; Wong TY et al., 2008; Sasongko BM et al., 2011). Albuminuria and smoking have positive association with DR but literature reveals inadequacy regarding CSME (The Diabetes Control and Complications Trial Research Group, 1993; Stratton IM et al., 2001; Jorge F Esteves et al., 2009). This study intends to determine the prevalence of CSME and to elucidate the influence of possible systemic risk factors like glycemic control, lipid fraction, albuminuria, hypertension and smoking in patients with DR with or without CSME.

Materials and methods

Study population

Patients with confirmed diagnosis of DM (type I and II) and DR who visited out-patient department of BP Koirala Lions Center for Ophthalmic Studies and In-patient ward of Internal Medicine department, Institute of Medicine who gave informed consent according to the declarations of Helsinki.

The patients with confirmed diabetes were included. The diagnosis of diabetes was made by an internist based on the following criteria (American Diabetes Association 2013).

- Fasting plasma glucose level >126 mg/dl (>7.0 mmol/l)
- Or 2 hr plasma glucose level > 200 mg/dl (>11.1 mmol/l) (after 75 gm of glucose intake)
- Or in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, random plasma glucose>200 mg/dl (> 11.1 mmol/l)
- Or HbA1C >6.5%

Assessment of Diabetic Retinopathy

After detailed history and anterior segment examination, complete posterior segment examination was done after dilating pupil with combination of 0.08 % Tropicamid and 0.5% Phenylephrine eye drop. Posterior segment examination was done with 20 diopter and 90 diopter Volk lenses with a Haag-Striet 900 Slit lamp biomicroscope.

Classification of diabetic retinopathy was done according to International Clinical Diabetic Retinopathy Severity Scale (Wilkinson CP et al., 2003).

Assessment of Clinically Significant Macular Edema (CSME)

Clinically Significant Macular Edema was defined in accordance with the ETDR Study (Early Treatment Diabetic Retinopathy Study Research Group, 1985) by the presence of a set of characteristics:

- retinal thickening at or within 500 μm of the centre of the macula
- hard exudates at or within 500 μm of the macula, if associated with thickening of adjacent retina, or
- a zone, or zones, of retinal thickening one disc diameter or larger, any part of which is within one disc diameter of the centre of the macula.

Those fulfilling the criteria of CSME as defined by ETDRS were included in Group I or CSME group.

Those not fulfilling the criteria of CSME as defined by ETDRS, but with any grade of DR were included in Group II or Non-CSME group for the purpose of the study.

Patients were subjected to Fundus photography, Fundus Fluorescein Angiography (FFA) and Optical Coherence Tomography (OCT) of macula, where needed.

Assessment of glycemic control

Glycemic control was evaluated by testing HbA1C level using gel precipitation method.

Grading: Values vary from lab to lab due to lack of consensus, but below is a common
value system based on Diabetes Control and Complications Trial (DCCT).
• Normal range: 4.2- 6.2%
• Good control: 6.3- 6.8%
• Fair control: 6.9- 7.6%
• Poor control: >7.6%

Assessment of lipid profile
  – Recorded by photometric enzymatic methods
  Hypercholesterolemia was diagnosed if the serum cholesterol level was ≥ 240 mg/dl (6.15mmol/l) or if the patient was receiving treatment for hypercholesterolemia. The serum triglyceride level was considered high if it was ≥ 200 mg/dl (2.24mmol/l). The serum LDL cholesterol level was considered high if it was ≥ 190 mg/dl (4.87mmol/l). The serum HDL cholesterol level was considered low if it was ≤ 40 mg/dl (1.02 mmol/l) (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults2001).

Assessment of diabetic nephropathy
It was done by looking for presence of albumin in urine with the help of immunoturbidimetric method. It was diagnosed when albumin excretion rates exceeded 200μg/min (American Diabetes Association 2013).

Assessment of hypertension
Hypertension was defined according to Joint National Committee 7 as blood pressure value ≥ 140/90 mm Hg or with a history of use of antihypertensive drug (The JNC7 report, 2003).

Smoking history
History regarding smoking, whether they were current, past or non-smoker was elicited.

Statistical methods
The data were entered in database for statistical analysis. SPSS version 19 was used. Statistical significance was tested by using Chi-square test and Fischer-Exact test where indicated. Statistical significance (p value) was set at < 0.05.

Results
In this study, 110 DR patients were included.

Part I results
Results have been shown in following tables.

Table 1: Demographic data

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Mean age</td>
<td>53.5 ± 10.8 years</td>
</tr>
<tr>
<td>Male</td>
<td>74 (67.27%)</td>
</tr>
<tr>
<td>Female</td>
<td>36(32.72%)</td>
</tr>
<tr>
<td>M: F</td>
<td>2.05:1</td>
</tr>
<tr>
<td>Current or past smoker</td>
<td>47 (42.7%)</td>
</tr>
<tr>
<td>Non smoker</td>
<td>63 (57.3%)</td>
</tr>
</tbody>
</table>

CSMExisted most commonly with severe NPDR (46.66% in RE and 61.29% in LE) as illustrated in table 2.

Table 2: Relationship between CSME and Grading of DR

| CSME in RE (n=30) | Mild NPDR 4/30 (13.33%) | Moderate NPDR 5/30 (16.66%) | Severe NPDR 14/30 (46.66%) | PDR 7/30 (23.33%) |
| CSME in LE (n=31) | Mild NPDR 0/31(0%) | Moderate NPDR 6/31 (19.35%) | Severe NPDR 19/31 (61.29%) | PDR 6/31 (19.35%) |

Part II results: Risk factor analysis in two groups of study

Table 3: Persons with CSME

| Total number of persons with CSME in one or both eyes (group I/ CSME) | 40 (36%) |
| Total number of persons with CSME in none of the eyes but with any DR (group II/ Non CSME) | 70 (64%) |
Table 4: Prevalence of different risk variables in diabetic retinopathy with or without CSME

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I (CSME) n= 40</th>
<th>Group II (Non-CSME) n= 70</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>18 (45%)</td>
<td>41 (58.57%)</td>
<td>0.716 (Chi square)</td>
</tr>
<tr>
<td>Coexistent HTN</td>
<td>16 (40%)</td>
<td>38 (54.28%)</td>
<td>0.14 (Chi square)</td>
</tr>
<tr>
<td>HbA1C</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Normal</td>
<td>4 (10%)</td>
<td>19 (27.14%)</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>6 (15%)</td>
<td>17 (24.28%)</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>15 (37.5%)</td>
<td>12 (17.14%)</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>15 (37.5%)</td>
<td>22 (31.42%)</td>
<td>0.0264 (Fischer exact)</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>23 (57.5%)</td>
<td>38 (54.28%)</td>
<td>0.744 (Chi square)</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>28 (70%)</td>
<td>65 (92.86%)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>12 (30%)</td>
<td>5 (7.14%)</td>
<td>0.001 (Chi square)</td>
</tr>
<tr>
<td>Serum TG</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Normal</td>
<td>29 (72.5%)</td>
<td>46 (65.71%)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>11 (27.5%)</td>
<td>24 (34.29%)</td>
<td>0.462 (Chi square)</td>
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<tr>
<td>Serum LDL</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Normal</td>
<td>12 (30%)</td>
<td>28 (40%)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>28 (70%)</td>
<td>42 (60%)</td>
<td>0.294 (Chi square)</td>
</tr>
<tr>
<td>Serum HDL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>39 (97.5%)</td>
<td>63 (90%)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>1 (2.5%)</td>
<td>7 (10%)</td>
<td>0.253 (Fischer exact)</td>
</tr>
</tbody>
</table>

Discussion

The age of our study population ranged from 29 to 78 years, with a mean of 53.5 ±10.8 years, which was comparable to other studies (Shrestha MKet al, 2007; Thapa Ret al, 2012). Males were affected more (67.27%) than females (32.73%). Similar results were seen in other studies (Kohner EM et al,1998; Rajiv Raman et al, 2010; Thapa R et al, 2012). However, some studies showed female preponderance (Shrestha MKet al, 2007; G Paudyalet al,2008; Raba Thapaet al,2014). This concludes that DR has no sex predilection.

We found that 36% of the study population with DR had CSME which was higher than that reported by Shrestha MK (2007) (19.2%), Rajiv Raman (2010)(6.27%), Rehab Benarous(2011) (15.1%), and Thapa R(2014) (5.78%). The higher prevalence of CSME in our study could be because of poorly controlled diabetes, poor socio-economic background of the patients and delay in seeking treatment. Most of the other studies were conducted in general population and eye hospitals whereas ours was in a general tertiary care hospital where late presentation, poverty and comorbidities are more common.

In our study, most of the patients with CSME had severe NPDR. Similar results were observed in the study by Rajiv Raman (2010). This suggests a common pathological pathway between the two.

We found statistically significant association between CSME and poor glycemic control (p<0.05). Other studies have shown similar results (Klein R, et al 1998; Rajiv Raman, et al 2010; Rehab Benarous, et al 2011).

High serum cholesterol level showed significant association with CSME in our study which is comparable to other studies (Klein R et al,1998; Rajiv Raman et al, 2010; Rehab Benarous et al, 2011). LDL and TG levels were high and HDL levels low in our CSME patients. However, no statistical significance was found. Other studies have found significant association of CSME with high LDL and total cholesterol levels (Wong TY,etal 2008; Rajiv Raman, et al 2010).

Like Wisconsin Epidemiologic Study of DR (WESDR) (Klein R et al,1998),albuminuriawas not associated with increased risk of CSME in our study. Other studies point towards positive
association (Jorge F Esteves, et al 2009). Since microalbuminuria can precede the appearance of gross albumin in urine, microalbumin assessment rather than albumin in urine can be more sensitive.

As in other study (Rajiv Raman et al, 2010), no statistical significance was found between hypertension, smoking and CSME. On the contrary, studies such as WESDR (1998), DCCT(1993) have proposed that they are associated with increased risk of progression of DR. Hence, the results are conflicting.

A relationship between poor glycemic control and CSME could be explained by the vasodynamic changes brought about by accumulation of sorbitol and loss of pericytes in retinal capillaries (CrabbeMJet al, 1998). Likewise, a relationship between high total serum cholesterol and CSME could be due to associated endothelial cell damage; high serum cholesterol levels are known to cause endothelial dysfunction through a local inflammatory response, with consequent release of cytokines and growth factors (Landmesser U et al, 2000).

The concept of CSME is important as it generally represents the more severe end of the spectrum, leading to visual disability. The assessment of risk factors can help us analyze the predisposing conditions and thus direct us towards the treatment.

**Conclusion**

Poorer glycemic control and high serum total cholesterol level showed significant association with CSME.

Even though there were high LDL and TG and low HDL levels in patients with CSME as compared to those with no CSME, we did not find any statistical significance.

**References**


Suwal et al  
Diabetic retinopathy and macular edema  
Nepal J Ophthalmol 2015;7(14): 142-147

Diabetologia;44:156-63 


The seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure. The JNC7 report (2003). JAMA; 289 (19):2560-2571 


Source of support: nil. Conflict of interest: none