A Clinical Study on Correlation of Albuminuria with Different Stages of Diabetic Retinopathy

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1. Aims and Objectives

1.1 Aim

To study the correlation of albuminuria with different stages of sight threatening diabetic retinopathy

1.2 Objectives

Primary Objective
- To study the association of albuminuria with sight threatening diabetic retinopathy.
- To estimate the correlation of albuminuria with progression and treatment response in different stages of sight threatening diabetic retinopathy.

Secondary Objective
- To study the association of other systemic factors like HbA1c, Serum lipids with stages of sight threatening diabetic retinopathy

2. Materials and Methods

Prospective follow up case series done in Santhiram Medical College and General hospital, Nandyal.

The study was done from July 2017 to March 2019.

Inclusion criteria
- Patients with Type 2 diabetes mellitus referred from physician in Santhiram medical college and general hospital for DR screening.
- Patients with sight threatening diabetic retinopathy (i.e. severe NPDR with or without macular edema, PDR with or without macular edema).
- Patients willing to undergo treatment for diabetic retinopathy as and when required.
- Patients willing to come for follow-ups.

Exclusion criteria
- Pregnancy
- Accelerated Hypertension
- Patients with chronic kidney disease and patients on dialysis
- Patients with urinary tract infection (UTI)
- Patients with malignancies
- History of recent ocular surgeries
- Patients with ocular conditions that can lead to macular edema like retinal venous occlusion, intra-ocular surgery, inflammation, age related macular degeneration, serous chorioretinopathy etc

Sample Size
- The study recruited a total of 125 patients of diabetes mellitus with sight threatening diabetic retinopathy. 15 patients who did not come for follow up after contacting them 3 times over the phone or not willing to participate in the study were excluded from the study. So, a total of 110 patients were included in the study.
- The subjects were sorted into 2 groups which were, A) Patients with Severe NPDR which included 55 subjects, B) Patients with PDR which included 55 subjects.
- Patients in each group were again subdivided on the basis of presence of macularedema.
- The informed consent was obtained from the subjects after thoroughly explaining the purpose of the study to the subjects. Also the procedures that the subjects underwent were explained to them beforehand. The patients underwent baseline evaluations on the first visit and were followed up after 6 months of first visit.

Study type:
Prospective follow-up case series.
Study Period: July 2017 to March 2019

2.1 Methodology

- Written informed consent was taken from all patients prior to their inclusion in the study.
- Subjects recruited after being diagnosed as having diabetic mellitus as per American Diabetes Association criteria (ADA) 60 by the physician of the institute with blood tests like HbA1c, Serum lipid profile and urine routine including albumin.
- Patients underwent undilated and dilated fundus examination with 90 D and 20 D lens using slit lamp and Indirect ophthalmoscope after taking thorough history.
- Diabetic retinopathy was identified on comprehensive clinical examination.
- These subjects then underwent fundus photography, Optical Coherence Tomography (OCT) and Fluorescein angiography if required.
- Based on the findings of clinical and imaging modalities, Diabetic retinopathy in the subjects was classified according to the ICDS classification.
- Subjects were divided into three groups: Group 1 (severe NPDR), Group 2 (PDR) with or without macular edema.
- A spot urine albumin concentration > 61 was measured for the subjects in each group using Automatic calibrator machine in the hospital laboratory as advised by treating physician associated with the hospital.
- Also, fasting and post prandial blood sugar, Serum creatinine, Serum triglycerides, High Density Lipoproteins (HDL), Total cholesterol levels were noted for each subject from previous health record retrospectively which is of less than 1 month duration.
• Health records were taken from the hospital records as it is stored in the hospital medical record department.
• Depending on the values, patients were categorised as normoalbuminuria (< 20gm/L), micro albuminuria (20 - 200gm/L), and macro albuminuria (>200gm/L).
• Patients were given treatment as required (Intravitreal injection for patients with macular edema, Pan retinal photocoagulation for PDR patients, close observation and follow up every 2-3 months for SNPDR and PDR group, monthly for CSME patients).
• Patients were followed up at 6 months from the initial visit during which thorough fundus examination was performed along with repetition of the urinetests.

3. Performa of the Study

Table and chart showing various techniques employed and the values for various parameters for diabetic retinopathy

<table>
<thead>
<tr>
<th>Albuminuria</th>
<th>SNPDR</th>
<th>PDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>DME No DME</td>
<td>DME No DME</td>
<td></td>
</tr>
<tr>
<td>Normoalbuminuria</td>
<td>Microalbuminuria</td>
<td>Macroalbuminuria</td>
</tr>
<tr>
<td>Micro + Macro</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Method</th>
<th>Cutoff</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. Cholesterol</td>
<td>Photometric enzymatic method with reagent Peroxidase/4-aminooantipyrine/Phenol (PAP)</td>
<td>&gt;160mg/dl-Abnormal</td>
</tr>
<tr>
<td>S. Triglycerides</td>
<td>Photometric enzymatic method with reagent Glycerol Phosphate Oxidase-PAP</td>
<td>&gt;150mg/dl-Abnormal</td>
</tr>
<tr>
<td>S. LDL Cholesterol</td>
<td>Photometric enzymatic method with reagent Phosphotungstic acid</td>
<td>&gt;100mg/dl-Abnormal</td>
</tr>
<tr>
<td>S. HDL</td>
<td>Photometric enzymatic method (Caluculated)</td>
<td>&lt;40 for men, &lt;50 for women-Abnormal</td>
</tr>
<tr>
<td>CHOL/ HDL ratio</td>
<td>Photometric enzymatic method</td>
<td>&gt;5-Abnormal</td>
</tr>
</tbody>
</table>

- The diagnosis of Diabetes mellitus was made if Fasting blood sugar (FBS) was more than or equal to 126 mg/dl or 2 hour PostPrandial Blood Sugar (PPBS) was more than or equal to 200 mg/dl as per American Diabetes Association (ADA).
- Urine albumin is calculated from early morning mid-stream urine spot collection. Serum lipids and Serum Glycosylated Haemoglobin (HbA1c) was calculated from fasting venous blood sample.
- The cut offs for dyslipidaemia was taken as per National Cholesterol Education Programme (NCEP) 55 expert panel.
- In each group, a comparative analysis was performed and the relationship between different types of vision threatening diabetic retinopathy with grades of albuminuria, HbA1c levels and Serum lipids was studied.

4. Results

1) The study conducted was a prospective follow-upstudy.

2) The study involved a total of 110 patients with Type 2 diabetes with vision threatening diabetic retinopathy.
3) The subjects were sorted into 2 groups which were:
   - Pts with Severe NPDR with 55 patients with or without macularedema.
   - Pts with PDR with 55 patients with or without macularedema.
4) The patients underwent baseline evaluations on the first visit and were followed up after 6 months of first visit.

a) Demography

Age
In the study, mean age of subjects in the SNPDR group was 62.3 ± 7.9 years and among PDR group, the mean age was 60.5 ± 6.8 years. There was no significant difference in mean age between the two groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Nonproliferative Diabetic Retinopathy</td>
<td>62.3</td>
<td>7.9</td>
</tr>
<tr>
<td>Proliferative Diabetic Retinopathy</td>
<td>60.5</td>
<td>6.8</td>
</tr>
</tbody>
</table>

p = 0.189 Chi-Square test

Gender
In the study, in both the groups 29.1% subjects were females and 70.9% were males. No significant association between genders was seen between the two groups.

Majority of subjects in all the three groups were males.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Severe Nonproliferative Diabetic Retinopathy</th>
<th>Proliferative Diabetic Retinopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Male</td>
<td>39</td>
<td>39</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>Count</th>
<th>%</th>
<th>Count</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>16</td>
<td>29.1%</td>
<td>16</td>
<td>29.1%</td>
</tr>
<tr>
<td>Male</td>
<td>39</td>
<td>70.9%</td>
<td>39</td>
<td>70.9%</td>
</tr>
</tbody>
</table>

p = 1.000 Chi-Square test

Sex distribution N=55
b) Duration of diabetes
The mean duration of diabetes in SNPDR group was 16.9 ± 8.0 years and 17.0 ± 8.9 years in PDR group. No significant difference was observed in the mean duration of diabetes between two groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Duration of Diabetes in years</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Nonproliferative Diabetic retinopathy</td>
<td>16.9</td>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td>Proliferative Diabetic Retinopathy</td>
<td>17.0</td>
<td>8.9</td>
<td></td>
</tr>
</tbody>
</table>

P value 0.644

c) BCVA
- The median BCVA in the SNPDR group was 6/12 (range being 6/6 to HM +ve) and PDR group was 6/24 (range being 6/7.5 to HM+ve).
- A statistically significant difference was observed between the two groups in BCVA (p value=0.030)

d) CSME prevalence in Retinopathy group
Among the SNPDR group, 40% of the subjects had CSME and in PDR group 38.1% of the subjects of CSME.

<table>
<thead>
<tr>
<th>Group</th>
<th>SNPDR</th>
<th>PDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically significant Diabetic macular Edema</td>
<td>22</td>
<td>21</td>
</tr>
</tbody>
</table>

P value 1.000

e) Comparison of various parameters

(i) Systemic parameters
The mean values of FBS, PPBS, Total Cholesterol, LDL and HDL were more than normal in both the groups among SNPDR and PDR. The mean values of Hb, TG were in normal range in both the groups of SNPDR and PDR. No significant difference was observed in systemic parameters
among the two groups.

<table>
<thead>
<tr>
<th>SNPDR</th>
<th>PDR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>HB</td>
<td>13.5 (1.7)</td>
<td>13.4 (1.7)</td>
</tr>
<tr>
<td>FBS</td>
<td>156.0 (64.0)</td>
<td>160.8 (54.3)</td>
</tr>
<tr>
<td>PPBS</td>
<td>227.7 (76.0)</td>
<td>219.9 (70.2)</td>
</tr>
<tr>
<td>HbA1c</td>
<td>8.7 (1.8)</td>
<td>8.7 (1.6)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>190.3 (54.7)</td>
<td>180.1 (59.6)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>143.6 (59.1)</td>
<td>130.9 (62.7)</td>
</tr>
<tr>
<td>LDL</td>
<td>112.4 (45.4)</td>
<td>107.6 (47.3)</td>
</tr>
<tr>
<td>HDL</td>
<td>41.9 (7.9)</td>
<td>42.4 (7.2)</td>
</tr>
<tr>
<td>CHOL/ HDL</td>
<td>4.7 (1.3)</td>
<td>4.3 (1.3)</td>
</tr>
</tbody>
</table>

FBS, Cholesterol, LDL in clinically significant Diabetic macular edema group at baseline and after 6 months of follow up

Table and Bar diagram showing FBS, Cholesterol, and LDL in both groups

f) Glycaemic and lipid profile
In our study, majority of patients had elevated HbA1C and Total serum Cholesterol in both the SNPDR and PDR groups. Not much difference was present in other Serum lipid parameters. Majority of subjects in both the groups had normal Chol/HDL ratio. No statistically significant difference was observed in systemic parameters among the two groups.
Table and Bar diagram showing Glycemic and Lipid profile levels in both SNPDR and PDR subjects

\[ \text{HbA1c and Lipid profile} \]

- Proportion of patients with elevated levels in CSME
- Proportion of patients with normal levels in CSME

Among SNPDR subjects, both normal and microalbuminuric patients were equally distributed i.e. 34.5%, whereas among PDR subjects majority (54.5%) had Microalbuminuria.

- No statistical significance was observed between the groups and Urine albumin levels at baseline.

### Urine albumin at Baseline

<table>
<thead>
<tr>
<th>Condition</th>
<th>Normoalbuminuria</th>
<th>Microalbuminuria</th>
<th>Macroalbuminuria</th>
<th>Micro+Macro</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Count</strong></td>
<td><strong>%</strong></td>
<td><strong>Count</strong></td>
<td><strong>%</strong></td>
<td><strong>%</strong></td>
</tr>
<tr>
<td>Severe Nonproliferative Diabetic Retinopathy</td>
<td>19</td>
<td>19</td>
<td>17</td>
<td>36</td>
</tr>
<tr>
<td>Proliferative Diabetic Retinopathy</td>
<td>13</td>
<td>30</td>
<td>12</td>
<td>42</td>
</tr>
</tbody>
</table>

P value (Chi-square test) = 0.294.

Table and Bar diagram showing Association between Urine albumin levels in both the groups

**h) Progression of Severe Nonproliferative Diabetic Retinopathy**

Among the 55 cases in the SNPDR group, 10.5% of normoalbuminuric patients progressed to PDR, whereas 41.7% of albuminuric patients progressed to PDR. This difference between normal and albuminuric patients was statistically significant.
df = 2, p = 0.03* Chi square

Table and Bar diagram showing progression to PDR among normal and albuminuric patients

i) Resistance to treatment

- In the study, among 43 patients in both SNPDR and PDR group over a period of 6 months 41.6% of CSME subjects with normoalbuminuria were having persistent CSME.
- Similarly 80.6% of CSME subjects with Micro + Macroalbuminuria were having persistent CSME.
- Statistically significant association was observed between normo and albuminuric patients in CSME patients with regard to persistence of macularedema.

Table and Bar diagram showing patients showing resistant to treatment in CSME patients with respect to albumin levels.
5. Discussion & Conclusion

- Diabetic patients with proteinuria or those on dialysis usually present with severe forms of DR, but the association of DR with early stages of diabetic nephropathy has not been entirely established. Although microalbuminuria has been associated with an increased risk of proliferative DR in diabetic patients, this association is the subject of controversy for type 2 diabetic patients.
- In our study, 70.9% subjects were males, which were almost 3.5 times higher than percentage of females, which is 21.9%, in both the groups, and is similar to observation found in ACCORD study by A K MottL et al. (2014) which had 25% of females in severe DR group.
- In our study, the duration of DM was 16.9 ± 8.0 years in the SNPDR group and 17 ± 8.9 years in the PDR group. No statistically significant difference was observed among the two groups in terms of age.
- A statistically significant difference (p=0.030) was observed in the median BCVA of SNPDR group, which was 6/12 (6/6 to HM +nt) from that of PDR group, which was 6/24 (6/7.5 to HM+nt).
- In our study, majority of patients had elevated HbA1c, Serum total cholesterol (80% in SNPDR group, 91% in PDR group), HbA1c (70.9% in SNPDR group, 70.9% in PDR group). Majority of patients did not have elevated other serum lipid parameters. Majority of subjects in both the groups had normal Chol/HDL ratio. No statistically significant difference was observed in systemic parameters among the two groups.
- In our study, the mean values of FBS, PPBS, Total Cholesterol, LDL and HDL were more than normal in both the groups among SNPDR and PDR. The mean values of Hb and TG were in normal range in both the groups of SNPDR and PDR. But majority of patients did not have abnormal serum HDL and LDL levels. No significant difference was observed in systemic parameters among the two groups. These findings suggested that DR can be associated with elevated serum FBS, PPBS, HbA1c.

Albuminuria

- In our study, in the SNPDR group, 34.5% had normoalbuminuria, 34.5% had microalbuminuria, 31% had macroalbuminuria and 65.5% had both micro and macroalbuminuria; whereas in the PDR group, 23.6% had normoalbuminuria, 54.5% had microalbuminuria, 21.8% had macroalbuminuria and 76.4% had both micro and macroalbuminuria. Among SNPDR subjects, both normal and microalbuminuric patients were equally distributed i.e. 34.5%, whereas among PDR subjects majority (54.5%) had Microalbuminuria. No statistical significance was observed between two groups and Urine albumin levels at baseline.
- These findings suggested that patients with albuminuria are at a higher risk of developing severe stages of DR.

Progression of Severe Nonproliferative Diabetic Retinopathy

Among the 55 cases in the SNPDR group, 10.5% of normoalbuminuric patients progressed to PDR, whereas 41.7% of albuminuric patients progressed to PDR. This difference between normal and albuminuric patients was statistically significant (p = 0.030). This observation showed us that the patients with albuminuria are at a higher risk of progression to PDR compared to the patients of SNPDR with albuminuria and this is the novel finding discovered in our study.

Clinically significant macular EDEMA

- Among the SNPDR group, 40% had CSME and in the PDR group, 38.1% had CSME. In the study, among 43 patients of both SNPDR and PDR group over a period of 6 months 41.6% of CSME subjects with normal albuminuria were having persistent CSME. Similarly 80.6% of CSME subjects with micro and macroalbuminuria were having persistent CSME inspite of taking IntraVitreal injections (Anti VEGFs and Steroids) in both the groups.
- A statistically significant association (p = 0.024) was observed between normo and albuminuric patients in CSME patients with regard to persistence of macularedema.
- The above observation inferred that patients with albuminuric patients are resistant to treatment compared to patients with normoalbuminuria in CSME subjects.

6. Limitations of the Study

- Study was conducted with a small sample size even though adequate and done after calculating the sample size based on the prevalence of VTD in SouthIndia.
- Though it is a prospective study, it is a single centre study which is a tertiary eye care hospital. Recruitment of more subjects and involvement of multiple centres can help in cementing the results better.
- Single urine sample was used for albuminuria estimation, but other studies also used the same.
- Number of intravitreal injection taken were not standardized in patients with CSME.
- Follow up was done after 6 months and results were calculated which can be a short period for assessing the progression and treatment response in VTD patients.

7. Recommendations

- From the results of our study, we would like to conclude that sight threatening diabetic retinopathy patients with albuminuria to be followed up more frequently as they are more prone for the faster disease progression.
- The presence of albuminuria should warn the treating physician to refer the patients to ophthalmologists for early disease diagnosis and monitoring so that it can reduce the occurrence of irreversible visual loss due to DR.
- Large population based studies to be done to prove the correlation of albuminuria with early progression of the disease.

References


