

Study of Association between Diabetic Retinopathy and Diabetic Nephropathy

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Abstract

Original Research Article

Background: The number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014. Almost two-third of all Type 2 and almost all Type 1 diabetics are expected to develop diabetic retinopathy (DR) over a period of time. A close association between diabetic nephropathy and retinopathy exists in majority of patients, and one might entertain another cause for nephropathy in the absence of retinopathy. **Objectives:** to estimate the association between macular oedema in DM type 2 patients and diabetic nephropathy or Albuminuria (micro- and macroalbuminuria) and determine its role as a risk factor for presence and severity of DME. **Material and Methods:** This descriptive study was conducted in Department of Ophthalmology of tertiary care teaching hospital in north Maharashtra, India after obtaining ethical committee clearance. Patients with type 2 diabetes mellitus who presented to outpatient department and inpatients referred from other departments were evaluated as per inclusion and exclusion criteria. Demographic, general and clinical details were obtained which special emphasis on diabetes profile, ocular examination, pupil examinations and detailed urine examination. Statistical analysis: Mean, standard deviation, percentages and proportions were used for descriptive statistics. **Results:** Total 60 patients were included in the study. All patients were between 45 and 85 years with 17 patients in 45-55 years and 26 patients in 56-65 years, 12 patients in 66-75 years and 5 in 76-85 years range. Out of 60 patients, 34 were males and 26 females. The mean age in males was 60.8 ± 8.3 years and the mean age in females was 59.4 ± 7.6 years and the overall mean age was 60.3 ± 8.1 years. Among the 120 eyes of 60 patients studied, diabetic maculopathy was found in 92 eyes. As assessed by FFA focal macular edema was found in 35 eyes (38%), diffuse macular edema including cystoid macular edema was found in 29 eyes (31.5%), Ischaemic maculopathy in 11 eyes (11.9%) and mixed maculopathy in 17 eyes (18.6%). Out of 92 eyes with maculopathy, 34 eyes (36.6%) had severe NPDR, 24 eyes (25.4%) had very severe NPDR, 15 eyes (16.9%) had moderate NPDR, 10 eyes (11.3%) had low risk PDR and 9 eyes (9.9%) had high risk PDR. Urine Albumin concentration > 30 mg/24 hr or albuminuria was found in 28 patients (46.7%) and absent in 32 patients (53.3%). Urine albumin concentration > 30 mg/24 hr or albuminuria found significant difference or association with severity of diabetic macular edema ($p=0.039$). **Conclusion:** Patients with albuminuria (microalbuminuria or macroalbuminuria) are more likely to have diabetic retinopathy and diabetic macular edema as those without albuminuria. Microalbuminuria could be used as a risk marker for the development of diabetic macular edema.

Key Words: Diabetes Mellitus, Retinopathy, Nephropathy, Association.

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INTRODUCTION

The number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014. The global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014. Diabetes prevalence has been rising more rapidly in middle- and low-income countries. Diabetes is a major cause of blindness, kidney failure, heart attacks,

stroke and lower limb amputation. In 2016, an estimated 1.6 million deaths were directly caused by diabetes. Another 2.2 million deaths were attributable to high blood glucose in 2012[1].

India is set to emerge as the diabetic capital of the world. According to the WHO, 31.7 million people were affected by diabetes mellitus (DM) in India in the year 2000. This figure is estimated to rise to 79.4

million by 2030, the largest number in any nation in the world. Almost two-third of all Type 2 and almost all Type 1 diabetics are expected to develop diabetic retinopathy (DR) over a period of time [2].

A close association between diabetic nephropathy and retinopathy exists in majority of patients, and one might entertain another cause for nephropathy in the absence of retinopathy. One of the earliest publications to recognize the link between renal and retinal angiopathy was by Root *et al.* in 1954. [3] Microalbuminuria was linked to diabetes only in 1985 when Barnett *et al.* reported an association between these two conditions [4].

This study was carried out with objective to estimate the association between macular oedema in DM type 2 patients and diabetic nephropathy or Albuminuria (micro-and macroalbuminuria) and determine its role as a risk factor for presence and severity of DME.

METHODOLOGY

This descriptive study was conducted in Department of Ophthalmology of tertiary care teaching hospital in north Maharashtra, India after obtaining ethical committee clearance.

Source of Data

Patients who presented to our outpatient department and inpatients referred from other departments were evaluated as per inclusion and exclusion criteria and a total of 60 patients were selected for the study.

Inclusion Criteria

Patients who presented with following were included

- Patients reporting to ophthalmology OPD having age \geq 45 yrs with Type II (NIDDM) diabetes mellitus
- Diabetic retinopathy with clinically significant macular edema.
- DME with any level of diabetic retinopathy.
- Exclusion Criteria

The following cases were excluded from the purview of the study.

- Opacities of the media affecting vision – corneal, lenticular and vitreous opacities.
- Complications of diabetic retinopathy like – vitreous haemorrhage, retinal detachment and advanced diabetic eye disease.
- Cases with other macular diseases accounting for visual loss.
- Previous treatment for diabetic retinopathy – laser, IVTA.
- Contraindications for fluorescein angiography like known hypersensitivity and pregnancy.

- Patients with severe kidney disease or on renal dialysis

Sample size: This study included 60 patients with above mentioned criteria. with 120 eyes all having some form of CSME.

Procedure

- A case sheet is prepared noting the name, age, sex, address, occupation and income of the patients.
- Clinical history was recorded noting carefully –
 - age of onset of diabetes
 - duration of diabetes
 - symptoms of diabetes and its complications
 - history of treatment taken for diabetes
 - history of ocular treatment taken if any
 - history of hypertension etc.

Medical checkup of the patient done in detail

The patients were grouped as Type-II Non-Insulin dependent diabetes mellitus (NIDDM).

Subjects with type 2 diabetes were identified based on the American Diabete Association criteria.

Blood sugar level was monitored using glucometer and the patients were labelled as diabetic with-

- Fasting BSL more than 130mg/dl.
- Post prandial BSL more than 180 mg/dl.

The glucometer was calibrated every day and its reproducibility was assessed by measuring the blood glucose for the same patient six times and also with two machines

4. An elaborate ocular examination was performed. Biomicroscopic examination of the anterior segment was performed to identify any abnormality. The visual acuity was recorded for both distance and near without and with correction. The IOP was recorded by Goldmann's Applanation Tonometer.
5. The pupil was dilated using tropicamide and phenylephrine drops (phenylephrine avoided in patients who were hypertensive).
6. A detailed fundus examination was done by direct, indirect ophthalmoscope and slit lamp biomicroscopy using 90D Volk lens.
7. Retinal photographs were taken after pupillary dilatation (TOPCON fundus camera); all patients underwent 45° four-field stereoscopic digital photography. For those who showed evidence of any DR, additional 30° seven field stereo digital pairs were taken.
8. A morning urine sample was tested for albuminuria. Subjects were considered to have albuminuria, if the urinary albumin excretion was $>$ 30 mg/24 hours.
9. Microalbuminuria was measured by particle enhanced turbidometric inhibition assay on a spot

early morning urine sample and albumin excretion for 24 hours was then calculated.

10. Albuminuria estimation was done by a semi-quantitative procedure with the first morning urine sample by seimens uristix strips. The seimens uristix Microalbumin strip contains reagent areas that test for albumin in urine and provide semiquantitative results. In this study, only the albumin results were used. The albumin test is based on dye binding, using a high-affinity sulfonephthalein dye. At a constant pH, the development of any blue color is due to the presence of albumin. The resulting strip color ranges from pale green to aqua blue.
11. The patient was considered to have normoalbuminuria, if Urinary Albumin Excretion (UAE) was < 30 mg/24hour; significant albuminuria, if UAE was >30 mg/24 hours.
12. The diagnostic performance of measuring UAE in a spot morning urine sample in predicting albuminuria in subsequent 24-hour urine collections has been reported to be satisfactory

STATISTICAL ANALYSIS

Data was collected using a structured proforma on Excel software (Microsoft, Seattle, USA). Measurements were expressed as means and standard deviations for continuous variables and percentages for categorical variables and was analysed.

Ethical considerations

The study was conducted according to the Declaration of Helsinki; the protocol was reviewed and approved by the institutional ethics committee of the institute. A written informed consent was taken from all patients after explaining the procedure.

RESULTS

Total 60 patients were included in the study. All patients were between 45 and 85 years with 17 patients in 45-55 years and 26 patients in 56-65 years, 12 patients in 66-75 years and 5 in 76-85 years range. Out of 60 patients, 34 were males and 26 females. The mean age in males was 60.8 ± 8.3 years and the mean

age in females was 59.4 ± 7.6 years and the overall mean age was 60.3 ± 8.1 years.

In the study patients, the duration of diabetes mellitus ranged from 0-25 years. Among the 60 patients, 20 patients had diabetes mellitus since 6-10 years, 15 patients since 11-15 years, 10 patients since 16-20 years, 11 patients since less than 5 years and 4 patients from 20-25 years. Mean duration was 11.1 ± 6.1 years. Among the 60 patients, 42 patients (70%) were on oral hypoglycemic agents and 18 patients (30%) were on oral hypoglycemic agents and Insulin. Out of 60 patients of DME under study, 27 patients (45%) had unilateral DME whereas 33 patients (55%) had bilateral DME.

Table-1: Distribution of types of diabetic maculopathy (n=92)

Type of maculopathy	No. of eyes	Percentage
Focal	35	38%
Diffuse	29	31.5%
Ischaemic	11	11.9 %
Mixed	17	18.6%
Total	92	100%

Out of 92 eyes with maculopathy, 34 eyes (36.6%) had severe NPDR, 24 eyes (25.4%) had very severe NPDR, 15 eyes (16.9%) had moderate NPDR, 10 eyes (11.3%) had low risk PDR and 9 eyes (9.9%) had high risk PDR.

Table-2: Distribution of Patients having URINE ALBUMIN EXCRETION > 30 mg/ 24 hr (ALBUMINURIA) (n=60)

UAE > 30 MG / 24 hr	No. Of Patients	Percentage
Present	28	46.7%
Absent	32	53.3%
Total	60	100%

Among the 60 patients with diabetic macular edema, Urine Albumin concentration > 30 mg/24 hr or albuminuria was found in 28 patients (46.7%) and absent in 32 patients (53.3%).

Table-3: Distribution of Albuminuria according to severity of DME (n=60)

Type of macular edema	No. of patients with albuminuria	No. of patients without albuminuria	Total	Percentage of albuminuria
Mild Macular edema	5	11	16	17.9%
Moderate macular edema	6	12	18	21.4%
Severe Macular edema	17	9	26	60.7%
Total	28	32	60	100%

$P=0.039$; significant

Among the 60 patients with DME under study, 28 patients had albuminuria (proteinuria). Out of 28

patients with albuminuria, 5 patients (17.9%) had mild macular edema, whereas 6 (21.4%) and 17 patients

(60.7%) had moderate and severe macular edema respectively. Urine albumin concentration $>30\text{mg}/24\text{ hr}$ or albuminuria found significant difference or association with severity of diabetic macular edema ($p=0.039$) by applying chi-square test as statistical analysis tool.

DISCUSSION

In the present study all patients were between 45 and 85 years of age. The majority (43.3%) of them were between 56 and 65 years of age. Mean age in males was 60.8 ± 8.3 years and in females was 59.4 ± 7.6 years. Overall mean age was 60.3 ± 8.1 years. In the study by Lawson *et al.* [5] the mean patient age was 58 years (range 29-73 years). In the study by Sander *et al.* [6] the mean age of patients was 57 years (range 28-71 years). The study by Golubovic A [7], included 86 patients with mean age of 61.8 years (range 49-73 years) in males and 62.8 years (range 51-74 years) in females.

In the present study all patients had type 2 diabetes mellitus. In the study by Shetty KJ *et al.* [8] 30 of 56 patients had Type 2 diabetes and majority were in 5th decade. In the study by Lawson PM *et al.* [5] of 94 patients with untreated diabetic maculopathy the patients were predominantly Type 2 diabetics. In the present, gender distribution was with total of 34 males and 26 females. The study by Wani J *et al.* [9] was showing a slight predominance of females with an overall male:female ratio of 27:29. In the study of Golubovic Arsovska [7] a mild domination of females (55.8%) versus males (44.2%) was observed, but there was no statistical significant association with its presence.

In the present study, the duration of diabetes mellitus ranged from 0 year to 25 years with a mean duration of 11.1 ± 6.1 years. In the study by Shetty KJ *et al.* [9] the duration of diabetes in patients with diabetic maculopathy ranged from 8-18 years in type 2 diabetes (mean 12.7 years) and 16-21 years in type 1 diabetes (mean 18.7 years).

In the study by Lawson *et al.* [5] 32 of 94 patients had maculopathy diagnosed at or within 2 years of the diagnosis of diabetes. In the study by Wani JS *et al.* [9] 62% in Group I (patients having NPDR) and 88% in Group II (patients having PDR) had a duration of diabetes ranging between 6 and 15 years. The average duration of diabetes was 10.3 years and 11.1 years in Groups I and II respectively. In both groups, patients with maculopathy had an average duration of diabetes, greater than seen in subjects without maculopathy. In the present study of 60 patients 70% were on oral hypoglycemic agents and 30% on oral hypoglycemic agents + insulin. Sparrow *et al.* [10] found a slightly higher prevalence of maculopathy in patients without insulin treatment and the reduction of vision due to maculopathy was revealed in 10% of the population on insulin. In the study by Wani S *et al.* [9] in Group I

(patients with NPDR) 76.19% were controlled on various hypoglycemic agents and insulin respectively. There was significant difference statistically ($p=0.01$) among patients on oral hypoglycemic agents and on insulin. Diabetic maculopathy was classified into 4 types depending on fluorescein angiography findings. Out of the 120 eyes of 60 patients, 92 eyes showed diabetic maculopathy. Out of the 92 eyes, focal macular edema (38%) and diffuse macular edema including cystoid macular edema (31.5%) were seen predominantly. Ischaemic maculopathy (11.9%) and mixed maculopathy (18.6%) with a combination of focal and diffuse or focal and ischaemic were seen in the rest of the eyes.

Among the 60 patients under study, Urine Albumin excretion $> 30\text{ mg}/24\text{ hr}$ or albuminuria was found in 28 patients (46.7%) and absent in 32 patients (53.3%). Among the 60 patients with DME under study, 28 patients had albuminuria (proteinuria). Out of 28 patients with albuminuria, 5 patients (17.9%) had Mild Macular edema, whereas 6 (21.4%) and 17 patients (60.7%) had Moderate and Severe Macular edema respectively. Urine albumin excretion $>30\text{mg}/24\text{ hr}$ or albuminuria found significant difference or association with severity of diabetic macular edema ($p=0.039$). In the study conducted by VK Ajoy Mohan *et al.* [11], 306 patients were included in the study. DR of any grade was seen in 132 (43%) patients, hard exudate formation in 93/306 (30.4%) patients, CSME in 50/306 (16.3%) patients and proliferative DR in 26/306 (8.5%) patients. Duration of diabetes ($P < 0.001$), microalbuminuria ($P < 0.001$) and low hemoglobin ($P = 0.001$) were found to be highly significant risk factors for the development and increasing severity of DR as well as for CSME and hard exudate formation. Microalbuminuria is strong predictors for DR, CSME and hard exudate formation in type 2 diabetics even after correcting for duration of diabetes and other systemic risk factors. J.L. Chin, *et al.* [12] studied 32 patients, 23 with macular edema, and 9 without it and found that increased frequency of microalbuminuria (95.96 mg/day, $p=0.028$) and serum creatinin (1.97 mg/dL, $p=0.010$) occurred in the group of patients with macular edema. They found an important metabolic disbalance in most of the patients with diabetic macular edema, and a significant relationship between macular edema and microalbuminuria and stated that Microalbuminuria could be used as a risk marker for the development of diabetic macular edema. Sharva Pandya *et al.* studied 246 patients and found out of 110 patients having diabetic retinopathy 69 (52.2%) patients had microalbuminuria [13]. An independent association between microalbuminuria and non-proliferative diabetic retinopathy (NPDR) was observed in a study from Cameroon by Sonbngwi *et al.* [14]. Study done by Ahmed *et al.* [15] showed higher incidence of proliferative diabetic retinopathy in microalbuminuria, positive patients. In a study conducted by Padmaja K Rani *et al.* carried out in

Chennai, Tamil Nadu, India¹⁶ showed that every 6th individual in the population of type 2 diabetes is likely to have albuminuria. Subjects with microalbuminuria were around 2 times as likely to have DR as those without microalbuminuria, and this risk became almost 6 times in the presence of macroalbuminuria.

CONCLUSION

Patients with albuminuria (microalbuminuria or macroalbuminuria) are more likely to have diabetic retinopathy and diabetic macular edema as those without albuminuria. Study found an important metabolic imbalance in most of the patients, and a significant relationship between macular edema and microalbuminuria. Microalbuminuria could be used as a risk marker for the development of diabetic macular edema.

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