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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 diabeticretinopathy

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 diabeticretinopathy.

Secondary Objective

- To study the association of other systemic factors like HbA1c, Serum lipids with stages of sight threatening diabeticretinopathy

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 DRscreening.
- Patients with sight threatening diabetic retinopathy (i.e. severe NPDR with orwithout macular edema, PDR with or without macular edema).
- Patients willing to undergo treatment for diabetic retinopathy as and whenrequired.
- Patients willing to come forfollow-ups.

Exclusion criteria

- Pregnancy
- AcceleratedHypertension
- Patients with chronic kidney disease and patients ondialysis
- Patients with urinary tract infection (UTI)
- Patients withmalignancies
- History of recent ocularsurgeries
- 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 diabetesmellitus 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 55subjects, B)Patients with PDR which included 55 subjects.
- Patients in each group were again subdivided on the basisof 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 upafter 6 months of firstvisit.

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 totheir inclusion in thestudy.
- Subjects recruited after being diagnosed as having diabetic mellitus asper American diabetes association criteria (ADA) 60 by the physician of the institute with blood tests like HbA1c, Serum lipid profile and urine routine includingalbumin.
- Patients underwent undilated and dilated fundus examination with 90 D and 20 D lens using slit lamp and Indirect ophthalmoscope after taking thoroughhistory.
- Diabetic retinopathy was identified on comprehensive clinicalexamination.
- These subjects then underwent colour fundus photography, Optical Coherence Tomography (OCT) and Fluorescein angiography ifrequired.
- 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), Group2 (PDR) with or without macular edema.
- A spot urine albumin concentration61 was measured for the subjectsin 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 recordsretrospectively which is of less than 1 monthduration.

- 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 forSNPDR and PDR group, monthly for CSMEpatients)
- 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

Albuminuria	SNPDR		PDR	
	DME	No DME	DME	No DME
Normoalbuminuria				
Microalbuminuria				
Macroalbuminuria				
Micro + Macro				
Total				

Parameters	Method	Cutoff
S. Cholesterol	Photometric enzymatic method with reagent Peroxidase/4-aminoantipyrine/Phenol (PAP)	>160mg/dl-Abnormal
S. Triglycerides	Photometric enzymatic method With reagent Glycerol Phosphate Oxidase-PAP	>150mg/dl-Abnormal
S. LDL Cholesterol	Photometric enzymatic method With reagent Phosphotungstic acid	>100mg/dl-Abnormal
S. HDL	Photometric enzymatic method (Caluculated)	<40 for men, <50 for women-Abnormal
CHOL/ HDL ratio	Photometric enzymatic method	>5-Abnormal

- 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 bloodsample.
- The cut offs for dyslipidaemia was taken as per National Cholesterol Education Programme (NCEP) 55 expertpanel.
- 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 Serumlipids wasstudied.

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 andwere 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 agebetween the twogroups.

		Age	
		Mean	SD
Group	Severe Nonproliferative Diabetic retinopathy	62.3	7.9
	Proliferative Diabetic Retinopathy	60.5	6.8
P value		0.189	

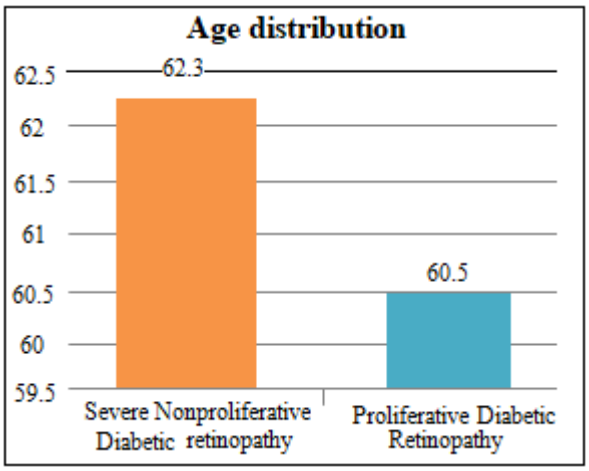


Table and Bar diagram showing Age distribution of subjects

Gender

- In the study, in both the groups 29.1% subjects were femalesand 70.9% were males. No significant association between genders was seen between the twogroups.
- Majority of subjects in all the three groups weremales.

Group		Severe Nonproliferative Diabetic retinopathy		Proliferative Diabetic Retinopathy	
		Count	%	Count	%
Gender	Female	16	29.1%	16	29.1%
	Male	39	70.9%	39	70.9%

p = 1.000 Chi- Square test

Sex distribution N=55

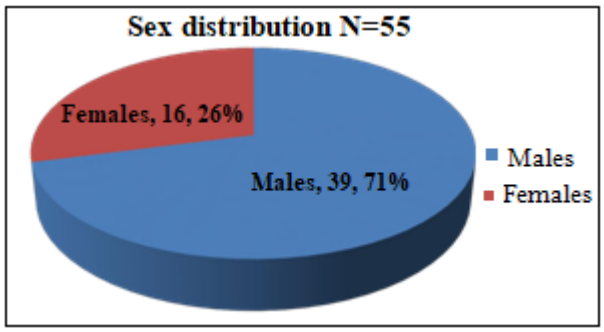


Table and pie diagram showing Gender distribution of subjects in both SNPDR and PDR groups

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.

		Duration of Diabetes in years	
		Mean	**SD**
Group	Severe Nonproliferative Diabetic retinopathy	16.9	**8.0**
	Proliferative Diabetic Retinopathy	17.0	**8.9**
P value		**0.644**	

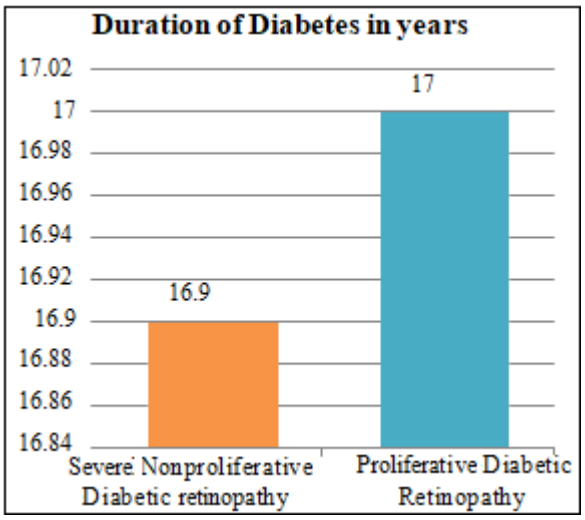
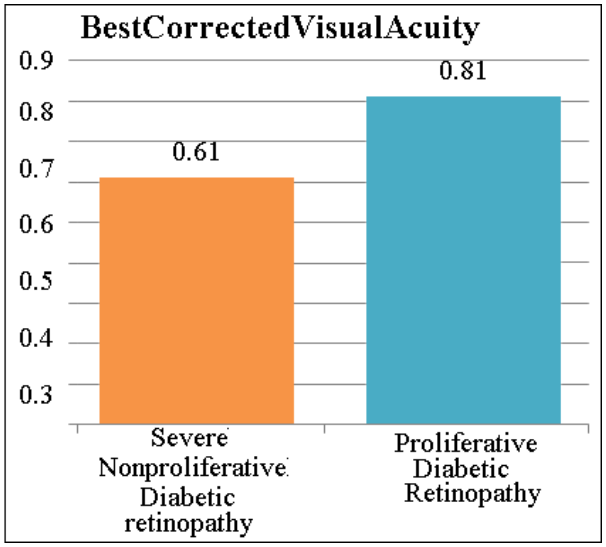


Table and bar diagram for duration of diabetes in various groups

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 inBCVA (p value=0.030)



Bar diagram showing Log MAR Best Corrected Visual acuity (BCVA) in both the groups.

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.

Group	SNPDR		PDR	
	Count	%	Count	%
Clinically significant Diabetic macular Edema	22	40.0%	21	38.1%
P value	1.000			

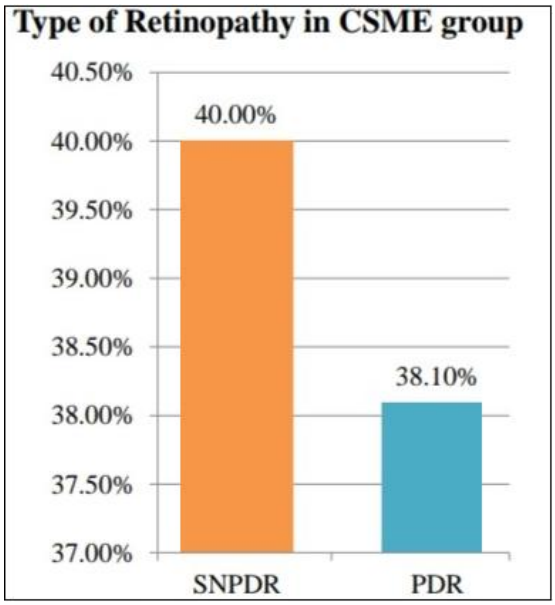


Table and Bar diagram showing Type of Retinopathy in CSME group

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.

	SNPDR		PDR		P value
	Mean	SD	Mean	SD	
HB	13.5	1.7	13.4	1.7	0.620
FBS	156.0	64.0	160.8	54.3	0.328
PPBS	227.7	76.0	219.9	70.2	0.605
HbA1c	8.7	1.8	8.7	1.6	0.469
Cholesterol	190.3	54.7	180.1	59.6	0.598
Triglycerides	143.6	59.1	130.9	62.7	0.111
LDL	112.4	45.4	107.6	47.3	0.622
HDL	41.9	7.9	42.4	7.2	0.535
CHOL/ HDL	4.7	1.3	4.3	1.3	0.151

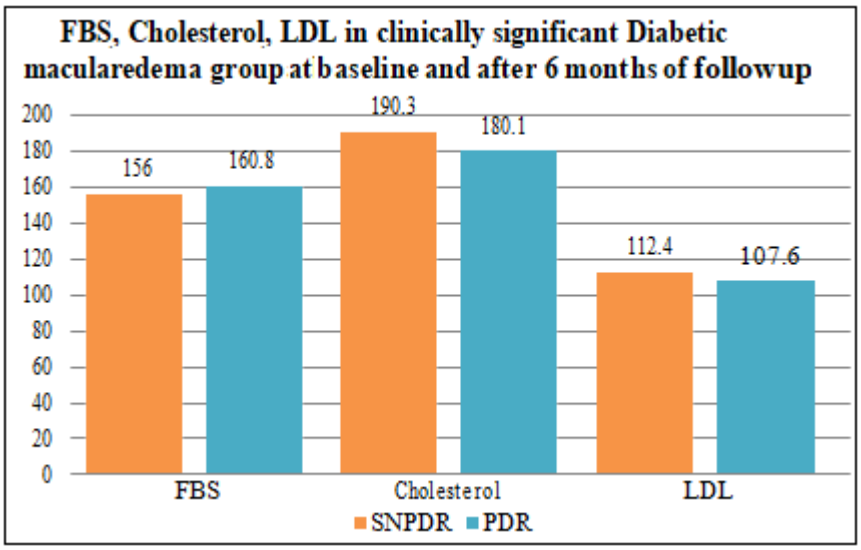


Table and Bar diagram showing FBS, Cholesterol, and LDL in both groups

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.

Systemic parameter	SNPDR		PDR		P value
	Normal	Elevated	Normal	Elevated	
HbA1C	11 (20.0%)	44 (80.0%)	05 (09.0%)	50 (91.0%)	0.175
Cholesterol	16 (29.0%)	39 (70.9%)	19 (34.5%)	36 (65.5%)	0.683
TG	31 (56.4%)	24 (43.6%)	40 (72.7%)	15 (27.3%)	0.110
LDL	24 (43.6%)	31 (56.4%)	31 (56.4%)	24 (43.6%)	0.252
HDL	28 (50.9%)	27 (49.0%)	32 (58.2%)	23 (41.8%)	0.566
Chol/ HDL	39 (70.9%)	16 (29.0%)	38 (69.0%)	17 (30.9%)	1.000

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

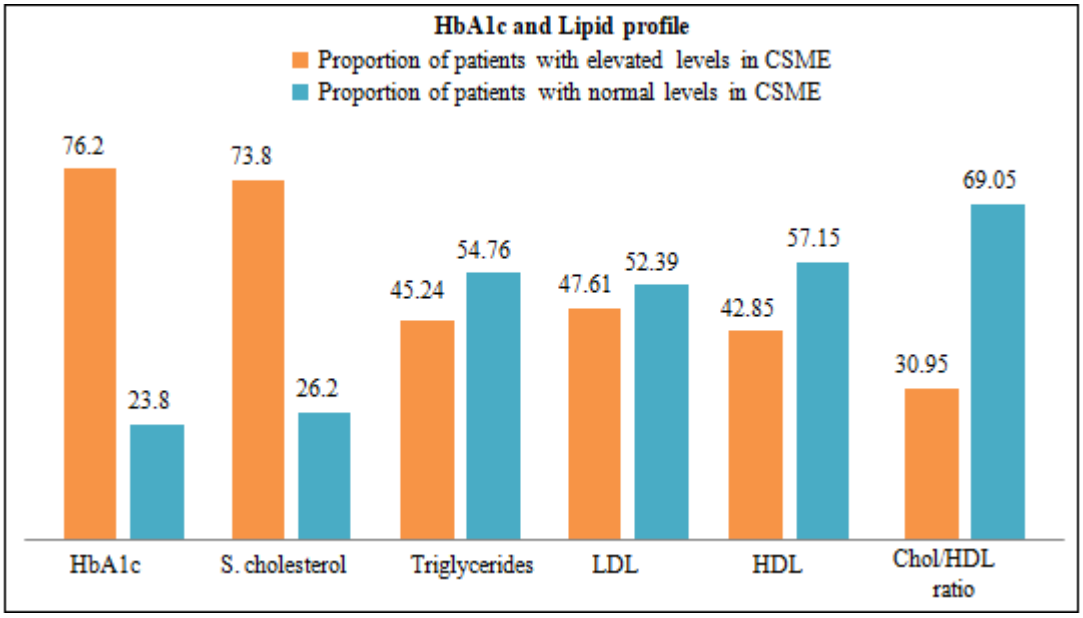


Table and Bar diagram showing Glycemic and Lipid profile levels in both SNPDR and PDR subjects

g) Association with UrineAlbumin

- 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							
	Normoalbuminuria		Microalbuminuria		Macroabluminuria		Micro+Macro	
	Count	%	Count	%	Count	%	Count	%
Severe Nonproliferative Diabetic retinopathy	19	34.50%	19	34.50%	17	30.90%	36	65.50%
Proliferative Diabetic Retinopathy	13	23.60%	30	54.50%	12	21.80%	42	76.40%

P value (Chi-square test) = 0.294

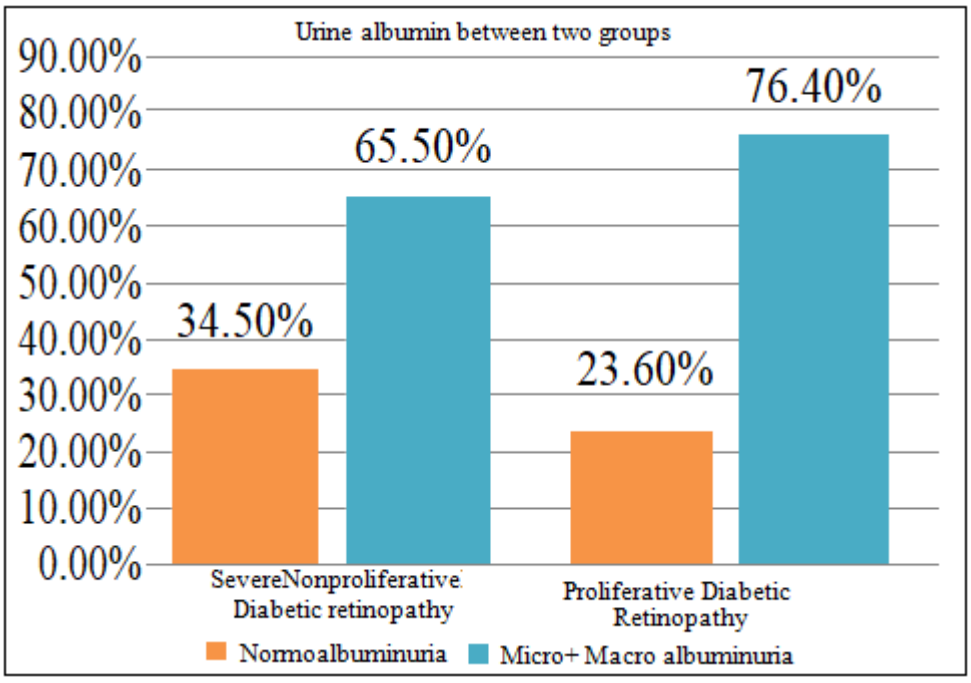


Table and Bar diagram showing Association between Urine albumin levels in both the groups

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.

		Progression tp PDR			
		Stable		Progressed	
		Count	%	Count	%
Group	Normoalbuminuric	17	89.5%	2	10.5%
	Micro & Macro albuminuric	21	58.3%	15	41.7%

df = 2, p = 0.03* Chi square

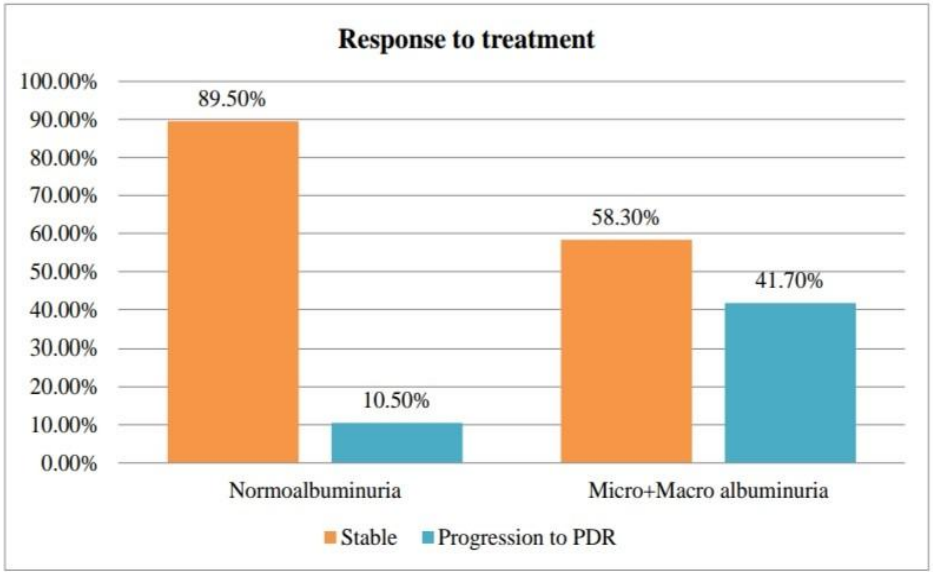


Table and Bar diagram showing progression to PDR among normal and albuminuric patients

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 + Macroabluminuria were having persistent CSME.
- Statistically significant association was observed between normo and albuminuric patients in CSME patients with regard to persistence of macularedema.

	Clinically Significant Macular Edema (CSME)		P value (Chi-Square)
	Resolved	Persisting	
Proportion of Normoal bumunuric patients	7/12 (58.3%)	5/12 (41.6%)	
Proportion of elevated albumin levels patients (micro+ macro)	6/31 (19.4%)	25/31 (80.6%)	0.024*

Number of elevated albumin levels patients (micro+ macro)

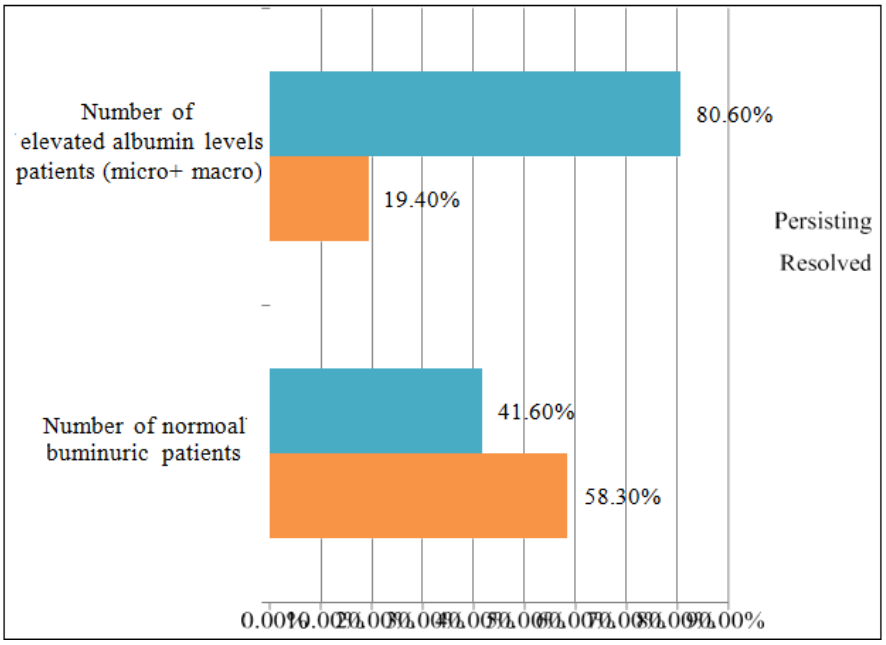


Table and Bar diagram showing patients showing resistant to treatment in CSME patients with respect to albumin levels.

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 ofdiabetic 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 issimilar to observation found in ACCORD study by A K MottL et al. (2014) which had 25% of females in severe DRgroup.
- 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 ofage.
- A statistically significant difference (p=0.030) was observed in themedian BCVA of SNPDR group, which was 6/12 (6/6 to HM +nt) from that ofPDR 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 twogroups.
- 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 valuesof 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 microalbumiuria, 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 atbaseline.
- These findings suggested that patients with albuminuria are at a higher riskof 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 normoalbuminuria werehaving persistent CSME. Similarly 80.6% of CSME subjects with micro and macroabluminuria 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 prevalenceof VTDR in SouthIndia.
- Though it is a prospective study, it is a single centre study which isa 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, butother studies also used thesame.
- Number of intravitreal injections taken were not standardized in patients with CSME.
- Follow up was done after 6 months and results were calculatedwhich can be a short period for assessing the progression and treatment response in VTDR 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 morefrequently as they are more prone for the faster diseaseprogression
- The presence of albuminuria should warn the treating physician to refer the patients to ophthalmologists for early disease diagnosis and monitoring sothatit can reduce the occurrence of irreversible visual loss due toDR.
- Large population based studies to be done to prove the correlation ofalbuminuria with early progression of the disease.

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