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Albuminuric Status in Patients with Clinical Diabetic Retinopathy in Type II Diabetes Mellitus

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Abstract
Introduction: *Aim of this study was to correlate diabetic retinopathy and its severity with type of albuminuria and renal status of the patients*
Methods: *In this observational correlative study 100 patients suffering from diabetes type II were examined. Fundus examination was performed. Ratio of urinary albumin to creatinine, serum potassium and HbA1C were measured. Fundus fluorescein angiogram was done in patients with clinical maculopathy and in patients with suspected PDR to confirm the diagnosis*
Results: *Among the study population, 53 participants were male and 47 were female. Majority of patients with clinical diabetic retinopathy of varying grades had microalbuminuria (57%) followed by normoalbuminura (25%) and macroalbuminuria (18%). The difference in the proportion of grade of diabetic retinopathy across albuminuria was statistically significant (p value <0.001). Among studied population PDR & advanced diabetic eye disease was found in 8% of normoalbuminura patients, 10.5% of microalbuminuria patients and 55.6% of macroalbuminuria patients. Urine microalbumin to creatinine ratio increased with severity of grade of retinopathy which was found to be statistically significant (P Value <0.001)*
Conclusion: *Macroalbuminuria was associated with severe grade of diabetic retinopathy in type II diabetic patients. Urine microalbumin to creatinine ratio was associated with increased severity of grade of retinopathy. Maculopathy was not associated with albuminuria in our study.*

Introduction

Diabetes mellitus (DM) is a complex chronic illness associated with a state of high blood glucose level, or hyperglycemia, occurring from deficiencies in insulin secretion, action, or both. The chronic metabolic imbalance associated with this disease puts patients at high risk for long-term macro- and microvascular complications.[1] Type-2 diabetes has become a pandemic worldwide especially in the elderly population aged more than 64 years. These patients have long disease duration and thus are associated with a higher risk of long-term complications, including diabetic retinopathy.[2]

Diabetic Retinopathy (DR) is the leading cause of preventable vision loss in adults and elderly. [3] Numerous studies have shown various risk-factors for DR that include poor glycemic control, hypertension, dyslipidemia, age of the patient, duration of diabetes, microalbuminuria, and cigarette smoking. [4]

Microalbuminuria is widely accepted as the first clinical sign of diabetic nephropathy. Current knowledge about the natural course of diabetic kidney disease is mostly derived from studies of patients with type 1 diabetes. As diabetic nephropathy progresses, the development of microalbuminuria eventually leads to macroalbuminuria and then to progressive loss of glomerular filtration rate (GFR). Among type 1 diabetic patients who have nephropathy, more than 95% will already have diabetic retinopathy.[2] Screening for microalbuminuria with a spot urine albumin/creatinine ratio has been recommended for identifying the early stages of diabetic nephropathy when physicians can manage to prevent the progression to renal failure.[5] Retinopathy is easily recognizable clinical manifestation and precedes the clinically manifest signs of nephropathy in same patient. The association between diabetic retinopathy and nephropathy is weaker in patients with type-2 diabetes mellitus as compared to type 1 diabetes. [6] Albuminuria remains the only biomarker for early diagnosis of diabetic nephropathy. Many cross sectional studies are done in general diabetic population to correlate the diabetic retinopathy and albuminuria but only few studies are done in patients with clinical diabetic retinopathy to correlate the degree of albuminuria with retinopathy. Hence the study was conducted to assess the association between severity Diabetic retinopathy and albuminuria among patients with Type-2 Diabetes mellitus.

Materials and Methods

This cross sectional study was conducted in the department of Ophthalmology, Chettinad Medical College, Chennai from March 2014 to march 2016. The study included Type 2 diabetes mellitus patients with diabetic retinopathy who attended their regular medical and ophthalmological checkups confirmed by Funds examination.

Patients with systemic hypertension(which is a individual risk factor for proteinuria and antihypertensive medications(which may decrease proteinuria), other kidney disease retinal vascular disease, acute febrile illness, UTI and heart failure (which may cause transient rise in albumin excretion) or patients with previous history of intraocular surgery were excluded from the study

A thorough history was taken regarding duration and severity of diabetes and any other associated systemic conditions was collected in the standard proforma. All patients were subjected to detailed fundus examination after pupillary dilatation with 90D. Fundus fluorescein angiogram was done in patients with clinical maculopathy (to know the type) and in patients with suspected proliferative diabetic retinopathy to confirm the diagnosis. Serum urea and creatinine levels were done before FFA and the test was carried out only if they are within the normal range. Other blood investigations like HbA1c levels, serum potassium was done. In all patients with evidence of diabetic retinopathy urine routine and urine micro albumin to creatinine ratio was done.

Statistical Methods

All Quantitative variables were checked for normal distribution using Shapiro wilk test. Normally distributed data was compared using t-test. For non-normally distributed data were compared across grade of diabetic retinopathy using Kruskal Wallis test. Association between hba1c and urine micro albumin to creatine ratio variables was assessed by calculating spearman rank correlation coefficient (r_s) and the data was represented in a scatter diagram. Categorical outcomes (grade of diabetic retinopathy and maculopathy) were compared across study groups (albuminuria) using Chi square test. P value < 0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.[7]

Results

A total of 100 subjects were included in the analysis.

Table 1: Summary of base line characteristics

Base line characteristics	Summary
Age in years (Mean ± S.D)	54.41 ± 8.8
Gender (N=100) (N & %)	
Male	53 (53%)
Female	47 (47%)
Duration of diabetes	9.24 ± 5.19
Grade of diabetic retinopathy (N=100) (N & %) [ETDRS GRADING]	
Mild NPDR	31 (31.00%)
Moderate NPDR	20 (20.00%)
Severe NPDR	31 (31.00%)
PDR	15 (15.00%)
Advanced diabetic eye disease	3 (3.00%)
Maculopathy (N=100) (N & %)	27 (27%)

The mean age of study population was 54.41 ± 8.8. Among the study population, 53(53%) participants were males and remaining 47(47%) participants were females. The mean duration of diabetes was 9.24 ± 5.19. Among the grade of diabetic retinopathy population, majority of 31% participants had mild NPDR & severe NPDR for each respectively, 20% participants had mild NPDR and 15% participants had PDR. Among the study population, 27% participants had maculopathy. (Table 1)

Table 2: Summary of lab parameters (N=100)

Lab parameters	Mean ± SD	Minimum	Maximum
HBA1C (%)	9.36 ± 2.05	5.00	15.00
Potassium	4.27 ± 0.64	2.60	5.70
Serum urea (mg/dl)	20.16 ± 11.39	0.97	48.00
Serum creatinine (mg/dl)	2.01 ± 2.21	0.50	14.00
Urine micro albumin to creatine Ratio in mg/gm	128.46 ± 190.59	4.00	913.00

The mean HBA1C of study population was 9.36 ± 2.05 % (range of 5 to 15 %). The mean potassium of study population was 4.27 ± 0.64 (range of 2.60 to 5.70). The mean Serum urea of study population was 20.16 ± 11.39 mg/dl (range of 0.97 to 48 mg/dl). The mean serum creatinine of study population was 2.01 ± 2.21 (range of 0.50 to 14 mg/dl). The mean Urine micro albumin to creatine ratio of study population was 128.46 ± 190.59 (range of 4 to 913).. (Table 2)

Table 3: Summary of urine analysis

Urine analysis	Frequency (%)
Albuminuria	
Macro albuminuria	18 (18.00%)
Micro albuminuria	57 (57.00%)
Normal albuminuria	25 (25.00%)

Among the study population, 18% participants had macro albuminuria, 57% participants had micro albuminuria and 25% participants had norm albuminuria. (Table 3)

Table 4: Comparison of grade of diabetic retinopathy with albuminuria & maculopathy (N=100)

Grade of diabetic retinopathy	Albuminuria			Chi square	P-value
	Norm albuminuria (N=25)	Micro Albuminuria (N=57)	Macro Albuminuria (N=18)		
Mild NPDR	14 (56%)	16 (28.1%)	1 (5.6%)	32.16	<0.001
Moderate NPDR	6 (24%)	11 (19.3%)	3 (16.7%)		
Severe NPDR	3 (12%)	24 (42.1%)	4 (22.2%)		
PDR & advanced diabetic eye disease	2 (8%)	6 (10.5%)	10 (55.6%)		
Maculopathy					
Yes	4 (16%)	17 (29.8%)	6 (33.3%)	2.132	0.344
No	21 (84%)	40 (70.2%)	12 (66.7%)		

Among the people with norm albuminuria, 14 (56%) people had mild NPDR, 6 (24%) people had moderate NPDR, 3 (12%) people had severe NPDR and 2 (8%) people had PDR & advanced diabetic eye disease. Among the people with microalbuminuria, 16 (28.1%) people had mild NPDR, 11 (19.3%) participants had moderate NPDR, 24 (42.1%) people had severe NPDR and 6 (10.5%) people had PDR & advanced diabetic eye disease. Among the people with microalbuminuria, 1 (5.6%) participant had mild NPDR, 3 (16.7%) people had moderate NPDR, 4 (22.2%) people had severe NPDR and 10 (55.6%) people had PDR & advanced diabetic eye disease, the difference in the proportion of grade of diabetic retinopathy across albuminuria was statistically significant (p value <0.001). Among the people with normoalubuminura, 14 (16%) people had maculopathy. Among the people with microalbuminuria, 17 (29.8%) people had maculopathy. Among the people with macro albuminuria, 6 (33.3%) people had maculopathy, the difference in the proportion of maculopathy

between albuminuria was statistically not significant (p value 0.344). (Table 4)

Table 5: Comparison of median urine micro albumin to creatine ratio across grade of diabetic retinopathy (N=100)

Grade of diabetic retinopathy	Urine micro albumin to creatine ratio in Median (IQR)	Kruskal Wallis test (P value)
Mild NPDR	29.60 (16 to 47)	<0.001
Moderate NPDR	33.50 (24.75 to 117.50)	
Severe NPDR	43 (35 to 98)	
PDR & advanced diabetic eye disease	336.50 (55.75 to 481.75)	

Among the people with grade of diabetic retinopathy mild NPDR median urine micro albumin to creatinine ratio was 29.60 (IQR 16 to 47). It was 33.50 (IQR 24.75 to 117.50), 43 (IQR 35 to 98) and 336.50 (IQR 55.75 to 481.75) among people with grade of diabetic retinopathy moderate NPDR, sever NPDR and PDR & advanced diabetic eye disease. The difference in the urine micro albumin to creatinine ratio across grade of diabetic retinopathy was statistically significant (P Value <0.001)

Figure 1: Scatter plots diagram of spearman rank correlation between urine micro albumin to creatine ratio and HbA1c in the study population (N=100)
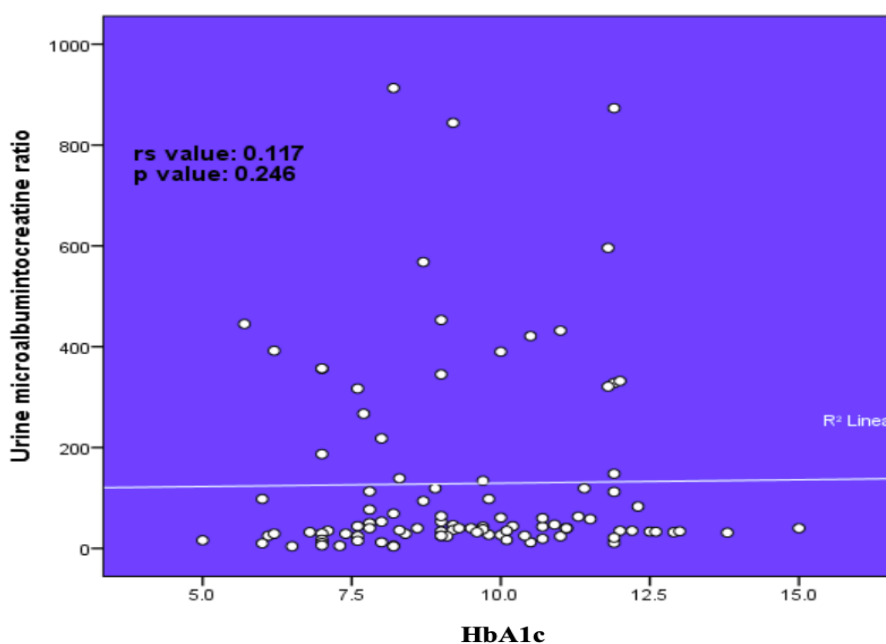
There was a weak positive correlation between urine micro albumin to creatine ratio and hba1c (r_s Value: 0.117, P value: 0.246)

Discussion

The current study chiefly reports the prevalence of albuminuria amongst subjects with type 2 diabetes and evaluates its role as a risk factor for Diabetic retinopathy.

In the present study, the age- and gender adjusted prevalence of diabetes mellitus in a population older than 40 years was 28.2%. Other studies have also shown a similar high prevalence of diabetes mellitus from India. In the current study, a total of 100 subjects were included in the analysis. The mean age of study population was 54.41 ± 8.8. 53(53%) participants were males and remaining 47(47%) participants were females. In the study by Ajoy Mohan, V., et al. [8] the mean age of the participants was 56.41 (± 10.01) with 193 (61.6) males and 113 (38.4) females. This was in accordance to the current study. In the study by Rani, P. K., et al[9] the mean age of the total study population (n = 1414) was 56.3 ± 10 yrs; 750 (53.04%) were men. This was also in accordance to the current study.

In the present study, the mean duration of diabetes was 9.24 ± 5.19. Majority 31% of participants had mild NPDR & 31% had severe NPDR for each respectively, 20% participants had mild NPDR and 15% participants had PDR. In the study by Somkiat Potisat, et al.[10] the mean duration of diabetes was about 5 years. In the same study No DR was found at 87.4% (125/143) in the normoalbuminuric group and at 80.4% (115/143) in the microalbuminuric group. Mild NPDR and moderate NPDR were 9.8% (14/ 143) and 7% (10/143) in the microalbuminuric group, respectively. Whereas, 7.7% (11/143) were mild NPDR and 4.9% (7/143) moderate NPDR were found in the normoalbuminuric group. The mean Diabetes duration (years) in the study by Boelter, M. C., et al [11] was 15.6 ± 8.5 with proliferative diabetic retinopathy and 10.1 ± 8.1 without proliferative diabetic retinopathy. In the study by Manaviat, M. R., et al [12] the duration of diabetes was less than 5 years in 30% of the patients, between 6–10 years in 30% and more than 10 years in 40% of them. Duration of diabetes was a

strong predictor of severity of retinopathy (p = 0.001). 39.3 % of the patients had retinopathy to some degrees, 19.2% had mild NPDR, 12% moderate NPDR, 2.7% severe NPDR and 5.4% had PDR.

The mean HBA1C of study population was 9.36 ± 2.05 %. The mean potassium was 4.27 ± 0.64 (range of 2.60 to 5.70). The mean Serum urea was 20.16 ± 11.39 mg/dl (range of 0.97 to 48 mg/dl). The mean serum creatinine was 2.01 ± 2.21. The mean Urine micro albumin to creatine ratio was 128.46 ± 190.59. In the study by Moriya, T., et al[13] HbA1c (%) (mmol/mol) was 8.3 ± 1.2 (67±13) and eGFR (mL/min/1.73 m2) was 86.0 ±25.2 respectively. Lee, W. J., et al.[14] in their study found that mean HbA1c, %, Creatinine, mg/dL and eGFR, mL/min/1.73m2 was 7.56 (1.50), 0.93 (0.45) and 83.36 (22.70) respectively. In the study by Ajoy Mohan, V., et al. [8] the mean (+SD) albumin excretion per day in patients with and without retinopathy was 688 (+99.6) g/day and 124.6 (+49.5) g/day respectively.

In the current study, 18% participants had macro albuminuria, 57% participants had micro albuminuria and 25% participants had norm albuminuria. In the study by Ajoy Mohan, V., et al. [8] the albuminuria was absent in 109 (36.0) , Microalbuminuria and Macroalbuminuria was present in 130 (42.2) and 67 (21.8) participants which was in accordance to the current study. In the current study it was also found that macroalbuminuria was associated with proliferative diabetic retinopathy & advanced diabetic eye disease in 55.6% participants. The macroalbumineria is seen as diabetic nephropathy progresses and the development of microalbuminuria eventually leads to macroalbuminuria and then to progressive loss of glomerular filtration rate (GFR).[2] The study by Abdelghaffar W et al.[15] showed an association between the degree of albuminuria and severity of retinopathy. About 97.5% of the macroalbuminuric patients had sight threatening forms of retinopathy (PDR + DM) compared with

87% of the microalbuminuric and only 15% of the normoalbuninuric patients.

In the current study population, 27% participants had maculopathy. 6 (33.3%) participants with macroalbuminaria was had maculopathy and 17 (29.8%) with microalbuminaria had maculopathy. However, there was no significant association found. In the study by Reddy, S. C., et al [16] retinopathy was seen in 36.5 % of type 2 diabetic patients with microalbuminuria; 7.3 % had proliferative retinopathy and 5.1 % maculopathy with microalbuminaria. Diabetic maculopathy is the most common micro vascular complication in diabetes causing visual impairment.[17] Our study findings were opposed to the findings by Aziz, K.[18] where levels of HbA1c, duration of diabetes, serum creatinine, microalbuminuria, spot urine protein and creatinine and their ratio (PCR) were significantly associated with maculopathy.

Among the mild NPDR diabetic retinopathy participants the median urine micro albumin to creatinine ratio was 29.60 (IQR 16 to 47). It was 33.50 (IQR 24.75 to 117.50), 43 (IQR 35 to 98) and 336.50 (IQR 55.75 to 481.75) in moderate NPDR, sever NPDR and PDR & advanced diabetic eye disease participants. The difference in the urine micro albumin to creatinine ratio across grade of diabetic retinopathy was statistically significant (P Value <0.001). There was a weak positive correlation between urine micro albumin to creatine ratio and hba1c (r_s Value: 0.117, P value: 0.246). Aziz, K.[18] in his study concluded that severity (grading) of retinopathy increases with the advancement of duration of diabetes, HbA1c , serum creatinine, microalbuminuria, spot urine protein, and blood pressure (systolic and diastolic). This was in accordance to the current study.

In the current study it was seen that Macroalbuminuria was associated with severe grade of diabetic retinopathy. As diabetic nephropathy progresses, the development of microalbuminuria leads to macroalbuminuria and then to progressive loss of glomerular filtration rate (GFR).[2] Thus it is but obvious that macroalbuminuria was associated with severe grade of diabetic retinopathy. Rani, P. K., et al.[9] in their regression analysis found that individuals with macroalbuminuria in comparison to micro- or normoalbuminuria showed a greater prevalence of DR (60.5% vs. 31.0% vs. 14.1%, p < 0.001), and also a greater severity of the disease (60.9% vs. 21.4 vs. 9.9, p < 0.001). They concluded that every 6th individual in the population of type 2 diabetes is likely to have albuminuria and 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.

The microvascular damage in type II diabetic patients goes hand in hand in retinal and renal vessels, thus excretion of albumin in urine can be regarded as a sign of kidney involvement and can reflect retinal vessels damage.[15]. Patients with micro- and macroalbuminuria are more likely to have Diabetic Retinipathy compared with those without albuminuria. Further longitudinal studies are required to confirm these findings.

Conclusion

Macroalbuminuria was associated with severe grade of diabetic retinopathy in type II diabetic patients. Urine microalbumin to creatinine ratio was associated with increased severity of grade of retinopathy.

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