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STUDY OF RELATIONSHIP BETWEEN ALBUMINURIA AND FUNDUS FINDING OF TYPE 2 DIABETES MELLITUS

***[1]Dr. Ankita Bhattacharya and [2]Dr. Ashok Kumar Maity**

[1]Assistant Professor, KPC Medical College and Hospital.
[2]Professor & HOD, Department of Ophthalmology, KPC Medical College and Hospital.

***Corresponding Author: Dr. Ankita Bhattacharya**
Assistant Professor, KPC Medical College and Hospital.

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ABSTRACT

Background: The prevalence of diabetic retinopathy in general population of India is 3.5% and its ubiquity in population with diabetes mellitus is 18%. At any level of retinopathy, the structure of macula may get altered leading to significant dysfunction due to development of Diabetic Maculopathy. Treatment of established retinopathy can reduce the risk of visual loss by 60%. Once diabetic maculopathy develops, there is no satisfactory treatment and the prognosis is very poor, so it is better to prevent its development. In this study, we have estimated different biochemical parameters of blood in all the participants to evaluate the effect of renal related assays on development and severity of diabetic retinopathy and diabetic maculopathy. **Method:** Study includes 100 case (diabetic retinopathy) and 100 control(diabetes without retinopathy)subjects. Further, case group was subdivided into subgroups according to its severity and depending on the presence of maculopathy. Thereafter, values of different renal parameters were compared between these sub groups. **Result:** Renal parameters (Blood Urea, Serum Creatinine) had not shown any statistically significant correlation either with severity of Diabetic retinopathy or CSME patients. Although, raised Urea and Creatinine levels exhibited relevant link with occurrence of DR. However, albuminuria established impressive association with severity of Diabetic retinopathy but not with CSME.

KEYWORDS: Diabetic Retinopathy, Maculopathy, ACR, Diabetic Nephropathy.

INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterised by hyperglycaemia resulting from defects in insulin secretion, insulin action or both. The chronic hyperglycaemia of diabetes is associated with long-term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels. Diabetes causes many complications. Diabetic retinopathy (DR) is the most common micro vascular complication in diabetes, which can produce severe visual loss. It is estimated that diabetes mellitus affects 4% of whole population, almost half of whom have some degree of diabetic retinopathy at a given time.[1,2] According to WHO, diabetic retinopathy is responsible for 3%-7% of total blindness in Asia.[3] In India, the prevalence of diabetic retinopathy in general population is 3.5% and the prevalence of diabetic retinopathy in population with diabetes mellitus is 18%.[4] In a population-based study in South India, diabetic retinopathy was detected in 1.78% of diabetic patients screened.[5,6]

Diabetic retinopathy is primarily classified into non-proliferative DR (NPDR), formally termed simple or background, and proliferative DR (PDR). Progression from mild, characterised by increased vascular permeability to moderate and then to severe and very severe NPDR characterised by vascular closure and increased risk for the development of PDR distinguished by the growth of new blood vessels on the retina and post surface of the vitreous.[7] Diabetic maculopathy is a form of diabetic retinopathy, in which visual loss occur due to macular oedema. It predominantly occurs in non-insulin dependent diabetics. Diabetic maculopathy can occur at any level of retinopathy and alter the structure of macula, significantly affecting its function. Although, treatment of established retinopathy can reduce the risk of visual loss by 60%. Once diabetic retinopathy or maculopathy occurs, there is no satisfactory treatment and the prognosis is very poor, so it is better to prevent its development. Hence, there is need to find out the risk factor associated with DR and CSME (Clinically significant macular oedema) and to control the same, reduces the incidence of visual loss in future. Data from many epidemiological studies support nephropathy as a

risk indicator and a risk factor and suggest that nephritic patients benefit from having regular ophthalmic evaluation. Conversely, presence of retinopathy is also a risk indicator of sub clinical nephropathy and these patient may benefit from screening for 24 hr urine protein estimation. Clinical diabetic nephropathy is primarily a consequence of ECM (extra cellular matrix) accumulation, due to imbalance between ECM production and rate of removal. The end of such accumulation is Glomerulosclerosis. There is also a component of Mesangial expansion which leads to capillary closure and scarring of glomeruli. Thus early predictor of diabetic retinopathy may aid in the prevention, delaying and progression and management of the disease. Assessment of renal parameters has been considered as one of the probable early predictors of diabetic retinopathy. In this study, we have estimated different biochemical parameters of blood in all the participants to evaluate the effect of renal related assays on development and severity of diabetic retinopathy, diabetic maculopathy.

MATERIALS AND METHODS

This case control study was conducted at Department of Biochemistry, KPC Medical College and Hospital, Kolkata for a period of one year. The study included 200 patients. Case group included 100 patients of diabetic retinopathy of > 18 yrs. of age attending Ophthalmology OPD. This case population was further categorised into 5 subgroups according to ETDRS criteria as follows: 1) Mild NPDR, 2) Moderate NPDR, 3) Severe NPDR, 4) Very severe NPDR and 5) PDR. This population was also subdivided on the basis of Maculopathy (CSME). 100 diabetic patients of Diabetes without diabetic retinopathy > 18 yrs. of age were taken as control. Sample size was taken conveniently.

Inclusion Criteria Included

1. Patients aged more than 18 years.
2. Patients having other systemic illnesses like hypertension and/or nephropathy and/or hyperlipidaemia.
3. Patients willing to participate in the study.

Exclusion Criteria Included

1. Patients who have had an episode of chronic inflammatory syndrome, alcoholism or malnutrition will not be included in the study.
2. Patient on diuretics, β-Blocker, hypolipidaemic agents or any other drug or hormone known to influence lipid or lipid protein metabolism will not be included.
3. Patients having familial hyperlipidaemia.
4. Non-diabetic cases of retinopathy (e.g. infective cause of retinal dystrophy, trauma, toxic maculopathy, ARMD).
5. Subjects not willing for consent.

The study protocol, informed consent and case record form were submitted to the Ethical Committee of K. P. C. Medical College and Hospital for approval. Informed consent was taken from all participants before inclusion in the study in a language of their own understanding. Illiterate individuals gave their finger-print (left-thumb impression) instead of signature. After obtaining ethical clearance and permission of Head of the Departments of Medicine and Biochemistry and appropriate authority, data collection was started by using pre-designed and pre-tested schedule, interviewing the participants, performing clinical examinations, laboratory investigations and record analysis. An informed written consent was obtained in every case. A detailed ocular history and medical history was taken. An elaborate biomicroscopic examination of the anterior segment was performed at ophthalmology OPD. Pupils were dilated with topical medication of 1% tropicamide and 5% phenylephrine drops, the later being omitted in hypertensives. Detailed fundoscopy was done by direct ophthalmoscopy, indirect ophthalmoscopy and slit lamp biomicroscope using 90D and 70D Volk lens. After fundus examination, only patients having retinopathy in at least one eye were selected for further study as case and subsequently divided on the basis of grade of DR and presence of maculopathy. Informed consent was taken from the concerned patients. The Diabetic retinopathy was graded according to ETDRS classification. Fasting venous blood was collected from the antecubital vein of each patient/ study subject in the fasting state (after overnight fasting of 12 hours) dispensed in clot activated and fluoride vial for estimation of urea, creatinine & Plasma Glucose. From the sample, serum and plasma was separated by centrifugation and stored at -20 degrees centigrade (C). Spot Urine of those patients were taken for measurement of ACR. The collected data were analysed with statistical software SPSS version 20. Data were normally distributed. So we applied independent ‘t’ test and One-Way ANOVA depending upon the number of groups compared. An alpha level of 5% has been taken, i.e. if any ‘p’ value is less than 0.05 it has been considered as significant.

RESULTS

As per ETDRS classification, Diabetic Retinopathy is divided into NPDR, Moderate NPDR, Severe NPDR, Very Severe NPDR and PDR. Volume of patients in successive order were 40, 33, 12, 4 and 11 respectively. Out of 100 Case Study patients, 69 of those were CSME negative and rest 31 subjects were CSME positive.

In this study, 80 patients had microalbuminuria. Among them 61% had DR. 15 patients among study population had macroalbuminuria and 100% of them had DR. So there is significant relationship between development of DR and albuminuria ($P<0.001$). Among Case group, 36% of patients had normal ACR and all of them were mild and moderate NPDR patients. 15% of patients among this group had macroalbuminuria and all of them were of severe, very severe NPDR and PDR patients. There was significant relationship between ACR and

severity of DR (P<0.001). But there was no significant relationship found between CSME and ACR(P=0.411).

Among 100 non-DR patients, 31 patients had developed diabetic nephropathy and on urine evaluation, microalbuminuria is detected. So we can conclude that in 31% patient diabetic nephropathy became earlier manifestation of micro vascular complication. In case group 36 patient show normal ACR value. That indicates in 36% case DR presented as early manifestation of microvascular complication of diabetes.

Table 1: Distribution of patients based on ACR in two groups studied.

		GROUP		Total		
		CASE	CONTROL		p Value	Significance
ACR	Normal	36(34.29)	69(65.71)	105	<0.001	Significant
	Microalbuminuria	49(61.25)	31(38.75)	80		
	Macroalbuminuria	15(100)	0(0)	15		

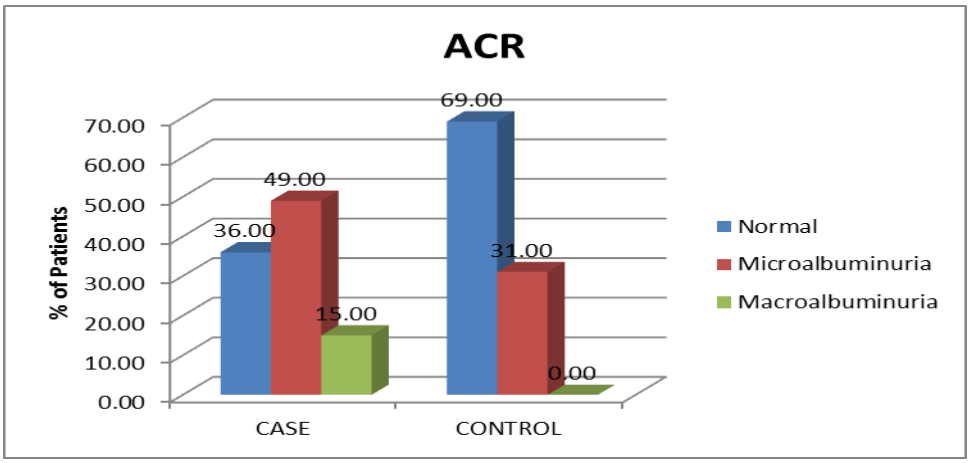

Fig 1: Distribution of patients based on ACR in two groups studied.

Table 2: Distribution of patients based on ACR in subjects categorized according to severity of diabetic retinopathy.

		Grade						
		Mild NPDR	Moderate NPDR	Severe NPDR	Very Severe NPDR	PDR	p Value	Significance
ACR	Normal	30(75)	6(18.18)	0(0)	0(0)	0(0)	<0.001	Significant
	Microalbuminuria	10(25)	27(81.82)	6(50)	2(50)	4(36.36)		
	Macroalbuminuria	0(0)	0(0)	6(50)	2(50)	7(63.64)		
Total		40(100)	33(100)	12(100)	4(100)	11(100)		

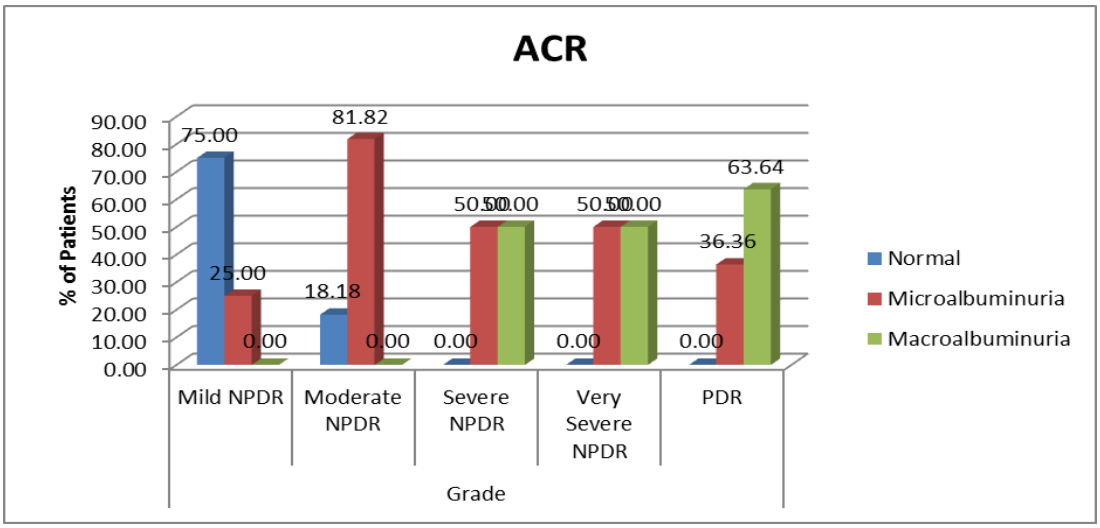

Fig 2: Distribution of patients based on ACR in subjects categorized according to severity of diabetic retinopathy.

Table 3: Distribution of patients based on ACR in subjects categorized depending on presence of CSME.

		CSME			
		Negative	Positive	p Value	Significance
ACR	Normal	26(37.68)	10(32.26)	0.411	Not Significant
	Microalbuminuria	31(44.93)	18(58.06)		
	Macroalbuminuria	12(17.39)	3(9.68)		
Total		69(100)	31(100)		

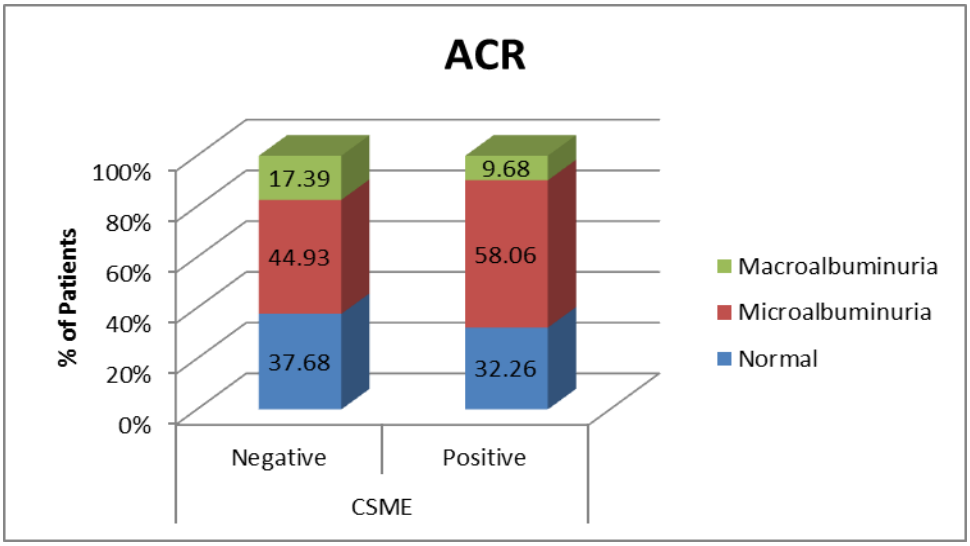

Fig-3: Distribution of patients based on ACR in subjects categorized depending on presence of CSME.

Comparison of Kidney parameters between two groups were studied. Mean value of blood urea in case was comparatively higher (41.24±24.01), than in control group (33.46±18.71) with a significant correlation coefficient of P=0.013. Mean value of Serum Creatinine in case group (1.25±0.88) was comparatively more than in Control group (0.98±0.36) with a significant correlation of P=0.009. Table 5 shows no significant correlation of Urea, Creatinine with severity of diabetic retinopathy (P=0.166 for urea, P=0.257 for Creatinine). Table 6 illustrates CSME positive patients had mean value of blood Urea (42.73±21.20) more than CSME negative patients (40.60±25.23) but without any significant correlation (P=0.410). Also mean value of blood Creatinine had no significant correlation with CSME(P=0.604).

Table 4: Comparison of Kidney parameters in two groups studied.

	GROUP					
	CASE		CONTROL			
	Mean	SD	Mean	SD	p Value	Significance
Ur	41.24	24.01	33.46	18.71	0.013	Significant
Cr	1.25	0.88	0.98	0.36	0.009	Significant

Table 5: Comparison of Kidney parameters according to severity of diabetic retinopathy.

	Grade											
	Mild NPDR		Moderate NPDR		Severe NPDR		Very Severe NPDR		PDR			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p Value	Significance
Ur	34.20	17.26	41.09	23.81	53.75	24.58	51.25	43.32	50.00	31.47	0.166	Not Significant
Cr	1.09	0.66	1.15	0.55	1.70	1.60	1.46	1.31	1.56	1.08	0.257	Not Significant

Table 6: Comparison of Kidney parameters depending on presence of CSME.

	CSME					
	Negative		Positive			
	Mean	Std. Deviation	Mean	Std. Deviation	p Value	Significance
Ur	40.60	25.23	42.73	21.20	0.410	Not Significant
Cr	1.28	0.93	1.18	0.75	0.604	Not Significant

DISCUSSION

In the present study, there were 100 diabetics in the No retinopathy group. Within this group, 69 patients had normal ACR levels in urine whereas 31 patients had microalbuminuria. In the mild NPDR group, 75% of the cases had normoalbuminuria and 25% of the cases had microalbuminuria. In the moderate NPDR group, 18.18% of the cases had normoalbuminuria and 81.82% of the cases had microalbuminuria. None of the patients in the above mentioned three groups had macroalbuminuria. However, moderate NPDR group had a large proportion of cases with microalbuminuria. In both severe and very severe NPDR group, one half of the cases had microalbuminuria while the other half had macroalbuminuria. In the PDR group, only 36.36% of the cases had microalbuminuria and the rest 63.64% of the cases had macroalbuminuria. None of the patients in the above mentioned three groups had normal albumin excretion. However, it can be observed that macroalbuminuria is seen in all the three groups. Also, major proportion of the PDR cases had macroalbuminuria. Statistical significance was found between ACR with severity of DR. ($P<0.001$). But no statistical significance was found between ACR and development of CSME ($P=0.411$).

This present study showed the comparison of Kidney parameters in two groups studied. Mean value of blood urea in case was comparatively higher (41.24±24.01), than in control group (33.46±18.71) with a significant correlation with $P=0.013$. Mean value of serum creatinine in case (1.25±0.88) was comparatively more than in control group (0.98±0.36) with a significant correlation with $P=0.009$. The study shows no significant correlation with urea, creatinine and severity of diabetic retinopathy ($P=0.166$ for urea, $P=0.257$ for creatinine). CSME positive patients had mean value of blood urea(42.73±21.20) more than CSME negative patients(40.60±25.23) but without any significant correlation ($P=0.410$). Also mean value of blood creatinine had no significant correlation with CSME ($P=0.604$).

The exact pathogenesis of frequent occurrence of PDR in diabetic nephropathy is not known. Since the retinopathy and nephropathy are linked together as ―microvascular in origin and share similar risk factors including the long duration of diabetes this occurrence can be explained. Similar to the retinal capillaries in DR, renal glomeruli also exhibit basement membrane thickening early in diabetic renal disease, resulting in characteristic nodular, diffuse and exudative glomerular lesions. The common end point of these renal lesions is glomerular hyalinisation, primarily an ischaemic event.[8] Also data from many epidemiological studies support nephropathy as a risk indicator and a risk factor and suggest that nephritic patients benefit from having regular ophthalmic evaluation. Conversely presence of retinopathy is also a risk indicator of sub clinical nephropathy and these patient may benefit from screening for 24 hr urine protein estimation. Early detection and treatment of nephropathy could reduce the mortality of such patients from other complications of nephropathy. Prevalence of Proliferative Retinopathy was significantly higher in patients with macroproteinuria as compared to those with microproteinuria. Gross proteinuria is a risk factor for Proliferative Retinopathy especially in younger onset diabetics. The presence of gross proteinuria at baseline has been reported to be associated with 95% increased risk of developing DME among type I patients in the WESDR. The prevalence of PDR was much higher in patients with persistent microalbuminuria.[9] Proteinuria was present in 29.2% of the subjects with DR in the CURES Eye study,[10] and studies from North India[11] have also suggested a correlation between DR and microalbuminuria.

CONCLUSIONS

The prevalence of advanced stages diabetic retinopathy was distinctly noticed in patients with macroalbuminuria in comparison to microalbuminuria that is skewing more towards the lower grades of retinopathy. In spite of the reality that a substantial proportion of diabetics without retinopathy also had microalbuminuria, this study suggests to implement Microalbuminuria and macroalbuminuria as a marker for detecting retinopathy and ophthalmic evaluation must be performed on such patients at the earliest. These observations are very much in concordance with other reviews. Albuminuria is significantly associated with development and severity of DR, but not with maculopathy. Raised Urea, Creatinine exhibited relevant link with occurrence of DR, but not with the severity of DR and maculopathy. Once diabetic retinopathy(specially diabetic maculopathy) occurs, there is no satisfactory treatment and the prognosis is very poor. So it is better to prevent its development. Hence to have a track on gravity of diabetic retinopathy, it is important to monitor the associated biochemical parameters regularly to reduce associated morbidity.

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