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Study to Assess Association of C - Reactive Protein with Nephropathy in People Living with Type 2 Diabetes Mellitus

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Kaushik Mondal*[1], Dattatreya Mukherjee[2], Debraj Mukhopadhyay[3]

[1]Calcutta National Medical College, Kolkata, West Bengal, India. [2] Jinan University, Guangzhou, P.R China [3]Department of Public Health, School of Allied Health Sciences, Delhi Pharmaceutical Sciences and Research University (DPSRU), Govt. of NCT Delhi, New Delhi - 110017, India.

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ABSTRACT

Introduction: **Diabetes mellitus** (DM) is a metabolic disorder with inappropriate hyperglycemia either due to an absolute or relative deficiency of insulin secretion or reduction in the biologic effectiveness of insulin or both. An inflammatory basis for Diabetes with its complications has attracted interest. Among several markers of inflammation, **C reactive protein** (CRP) is found to be significant in people with diabetes. Diabetic nephropathy may be associated with abnormally high levels of CRP. *Materials & Methods*: This study was performed for 1 year over 100 type 2 diabetic patients (n=100) aged 30-70 years in Calcutta National Medical College and Hospital. Necessary clinical & Diabetes related laboratory investigations were done as the routine procedure. *Results:* Among 100 study population, all macro-albuminuria patients were found to have high CRP. 63% of Stage 3 chronic kidney disease (CKD) patients were having high CRP in our study. High CRP values were also found among patients with higher spot urine ACR (329.50±259.40 mg/gram) (P<0.05). *Conclusion:* CRP is a marker which increased in inflammatory reactions. Low grade inflammation as indicated by high CRP was an important predictor of diabetic nephropathy.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder with inappropriate hyperglycemia either due to an absolute or relative deficiency of insulin secretion from beta cells of langerhans of endocrine part of pancreas or reduction in the biologic effectiveness of insulin or both or the outer receptors are malfunctioning. It is one of the most common non-communicable diseases worldwide and is a growing concern. Diabetes prevalence had increased by 64% across India over the last quarter century according to November 2017 report by Indian Council for Medical Research, Institute for Health Metrics and Evaluation, both research institutes and the Public Health Foundation of India, an advocacy. Genetics, Aging, Obesity, Lifestyles and many other factors have contributions to the development of Diabetes and its complications. Nevertheless, an inflammatory basis for Diabetes and its complications has attracted interest. Among several markers of inflammation, hs–CRP is found to be significant in people with diabetes. CRP, a pentameric protein produced by the liver has emerged as the 'golden marker for inflammation'. Proteinuria is a marker of vascular endothelial damage. Additionally, it is reported that high serum levels of CRP is a novel cardiovascular risk factor that impairs endothelial function. So diabetic nephropathy may be associated with abnormally high levels of CRP.

Diabetic nephropathy is a leading cause of CKD, Eend Sstage Rrenal disease (ESRD). It is diagnosed based upon the detection of proteinuria in diabetic patients in absence of other obvious cause such as infection **(**Rudy Bilous & Richard Donnelly: Handbook of Diabetes; 2010).

TABLE No. 1: Classifications of diabetic nephropathy with respect to albuminuria (Alvin C. Powers: Harrison's Principles of Internal Medicine; Diabetes Mellitus: Complications, McGraw Hill Education. 19thedition)

Urine specimen	Microalbuminuria	Macroalbuminuria
24 hour collection	30-299 mg/day	>=300 mg/day
Albumin concentration	20-300 mg/l	>300 mg/l
Spot albumin - creatinine ratio	30-300 mg/gram	>300mg/gram

In our study, we used spot urinary albumin-Creatinine ratio for detection of albuminuria. We

tested spot urine sample after excluding conditions that could transiently increase albumin excretion and same test was repeated 2 times at three months interval. If two out of three tests were positive, we considered the people having diabetic nephropathy.

Non-diabetes related conditions that might increase albuminuria are urinary tract infection (UTI), haematuria (RBC>5 RBC/hpf), prostate disease, heart failure, febrile illness, severe hypertension and vigorous exercise.

Microalbuminuria and macroalbuminuria may be present when patient is diagnosed of having type 2 DM first reflecting its long asymptomatic period. To institute effective therapy at an early stage, albuminuria should be detected. But some individuals with type 1 and type 2 DM have a decline glomerular filtration rate (GFR) in the absence of albuminuria. So measurement of the serum Creatinine & estimation of GFR should also be performed.

For patients with type 2 diabetes mellitus in NHANES III (THIRD NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY; n=1197), low GFR (60 ml/min /1.73 m^2) was present in 30% of patients in absence of micro or macroalbuminuria and retinopathy (Kramer, H.J., Nguyen, Q.D., Curhan, G. and Hsu, C.Y., 2003).

GFR can be measured by specific techniques, example-lnulin clearance. But the recommended equation by the National Kidney Foundation is that of the MDRD (Modified Diet In Renal Disease): estimated GFR (ml/min/1.73m^2)=186* (Serum creatinine in mg/dl)$^{-1.154}$ *(age in years)$^{-0.203}$. In female, it should be multiplied by 0.742.

Compared to MDRD formula, Inulin clearance slightly overestimates the glomerular functions. In early stage of renal disease, Inulin clearance may remain normal due to hyperfiltration in the remaining nephrons (GFR Cockcroft & MDRD Calculator at medical-calculator.nl).

GFR can also be accurately measured using radioactive substances, in particular Chromium-51 and Technetium-99m. These come close to ideal properties of Inulin but can be measured more practically with only a few blood or urine (Murray, A.W., Barnfield, M.C., Waller, M.L., Telford, T. and Peters, A.M., 2013).

Table No 2: Staging of Diabetic Nephropathy with respect to EGFR

Stage	e GFR (ml/min/1.73 m^2)
1	>=90
2	60-89
3A	45-59
3B	30-44
4	15-29
5	<15

But one point should also be noted that glomerular hyperperfusion and renal hypertrophy occur in the first years after the onset of DM and are associated with increase in GFR.

We did not include haemodialysis patients in our study as it was seen that there were some dialysis related alterations in the immune and host defense system. Moreover, the type of dialysis membrane had been suggested to play a role. So haemodialysis might exert an impact on C-Reactive protein level.

Creatinine clearance using CockCroft-Gault equation is less accurate. Creatinine clearance (ml/min)= {(140-age in years)* weight in kg}/(72* serum creatinine in mg/dl). It should be multiplied by 0.85 in females. Normal creatinine clearance for healthy men is 97-137 ml/min and for healthy women is 88-128 ml/min (Cockcroft, D.W. and Gault, H., 1976).

Nephropathy may be present due to conditions other than diabetes mellitus in people living with type 2 Diabetes. To establish diabetic nephropathy, some points should be kept in mind.

a) Duration of diabetes and glycemic status

b) Presence of hypertension

c) Associated retinopathy

d) Absence of haematuria and RBC (red blood cells) casts

e) Absence of strong family history of kidney disease due to etiology other than diabetes

f) Absence of rapid rise of creatinine.

We have only included patients clinically and biochemically suspected to have diabetic kidney disease. Normal blood value of CRP is considered as <4 mg/l according to laboratory reference range of our hospital.

Objectives

1. To correlate CRP level in relation to normoalbuminuria, micro-albuminuria and macro-albuminuria.

2. To correlate CRP protein levels with diabetic nephropathy based on estimated glomerular filtration rate.

3. To assess the influences of various clinical and biochemical factors on development of diabetic nephropathy.

MATERIALS AND METHODS

Total 100 type 2 diabetic patients (n=100) aged 30-70 years were studied for 1 year in Calcutta National Medical College and Hospital.

a) Inclusion criteria- Previously diagnosed or recently diagnosed type 2 Diabetes mellitus patients (age 30-70 years) were included in this study.

b) Exclusion criteria:

Patient with a history of urinary tract infections/ pyelonephritis, nephrolithiasis (kidney or bladder stone), catheterization, severe uncontrolled hypertension (HTN) (> 160/100 mm Hg), sickle cell anaemia, patients on haemodialysis, cancer (prostate, bladder and kidney), benign prostatic hypertrophy, polycystic kidney disease (PKD), prolonged use of analgesics, any recent infection which was caused by an infectious etiology and any type of surgery were excluded from the current study.

Inflammatory process like systemic lupus erythematosus, inflammatory bowel disease, rheumatoid arthritis, giant cell arteritis, osteomyelitis, rheumatic fever and tuberculosis were also excluded.

Clinical examinations and necessary laboratory investigations were done including blood for CRP, HbA1C, lipid profile, Creatinine and spot urine ACR. **CRP was measured by turbidimetry method**.

All statistical analyses were performed using Graph Pad Instat software (Version 3.10, 32 bit for Windows). The chi-square test and the Fisher exact test were used to evaluate the differences in proportions between the two groups. One way *ANOVA test* was used to compare groups for continuous variables. *Tukey Kramer Multiple Comparison test* was done after ANOVA if results were significant overall to find out which specific group's mean was different. P- Value<0.05 was taken as the level of significance.

RESULTS

TABLE No. 3: DISTRIBUTION OF CRP ACROSS THE RANGE OF PROTEINURIA

	CRP (<4 mg/dl) (n=44)	CRP (=> 4 mg/dl) (n=56)
Normoalbuminuria	16	1
Microalbuminuria	29	26
Macroalbuminuria	0	28

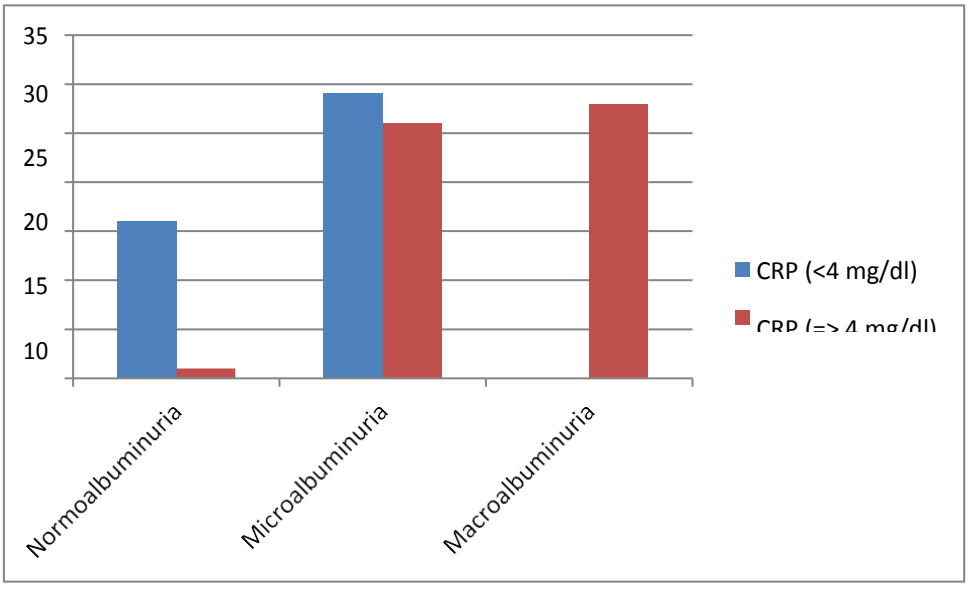

Figure No. 1: Bar diagram showing distribution of CRP across the range of proteinuria

TABLE No. 4: CRP DISTRIBUTION IN RELATION TO STAGES OF CHRONIC KIDNEY DISEASE BASED ON eGFR

	CRP<4 mg/dl (n=44)	CRP>4 mg/dl (n=56)
Stage 1	14	5
Stage 2	14	24
Stage3	16	27

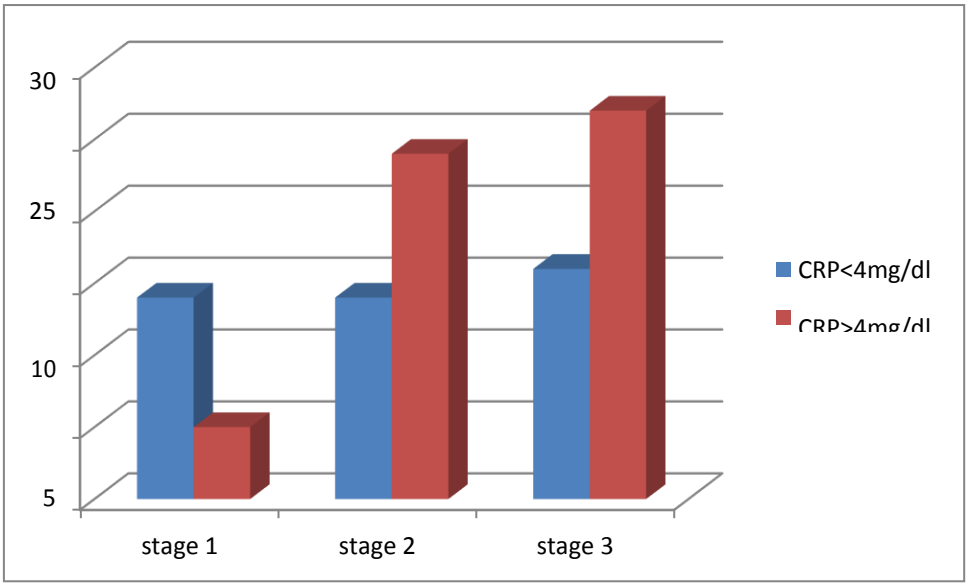

Figure No. 2: Bar diagram showing CRP distribution in relation to stages of chronic kidney disease based on eGFR

Table no 5: Relation between Diabatic nephropathy with respect to CRP

	CRP <4 mg/l	CRP>=4mg/l	P value
	(n=44)	(n=56)	
AGE (Year)	46.6±6.6	53.4±11.06	<0.05
BMI (kg/m^2)	22.75± 4.5	23.21±3.2	0.5
HbA1C (%)	6.45±1.42	6.75±0.831	0.2
Triglyceride (TG)(mg/dl)	102.02± 40.08	123.4±43.96	<0.05
LDL (mg/dl)	97.4± 33.47	113.45± 29.47	<0.05
Spot Urine ACR (mg/gram)	63.25±60.36	329.50±259.40	<0.05
Serum creatinine (mg/dl)	1.06± 0.3	1.16±0.29	<0.05

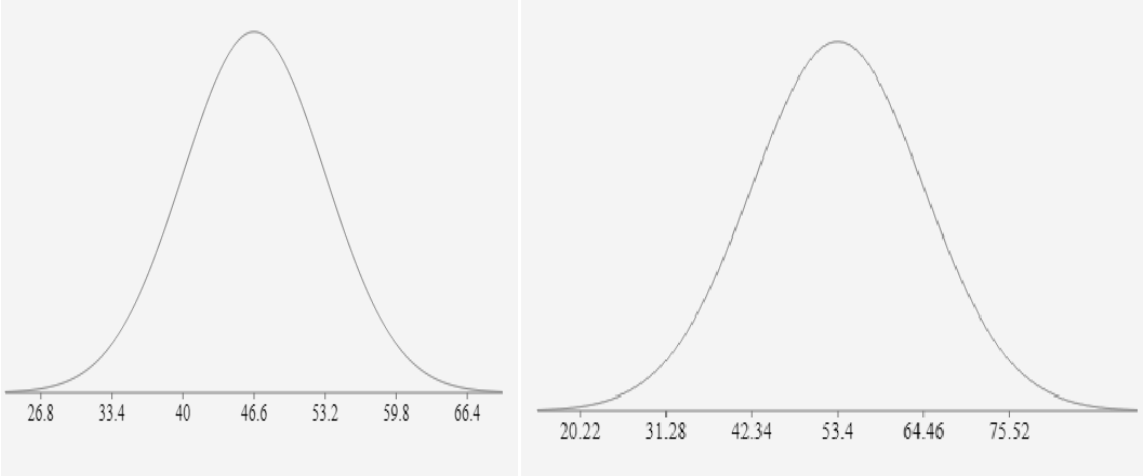

Figure No. 3: AGE DISTRIBUTION OF Crp<4 and Crp>=4

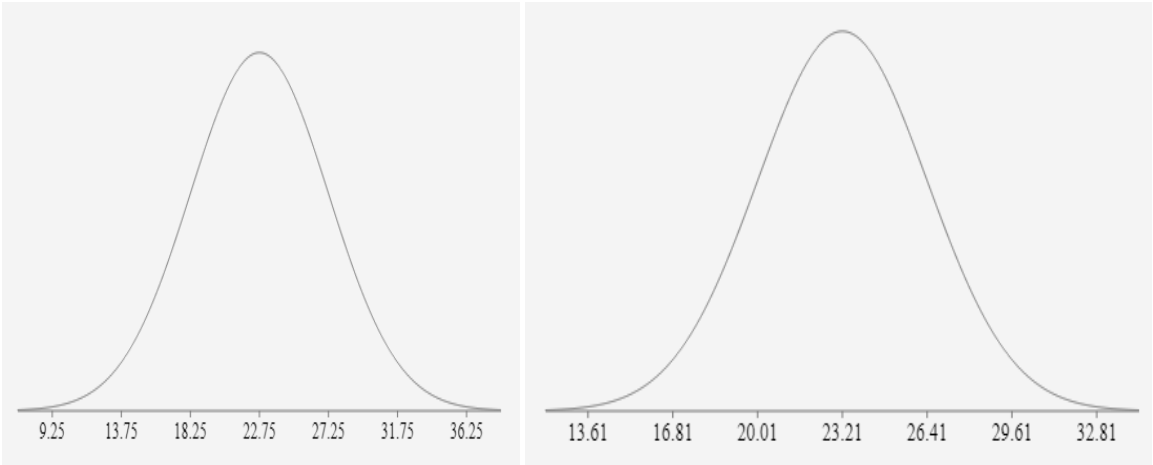

Figure No. 4: BMI Distribution of CRP<4 and CRP>=4

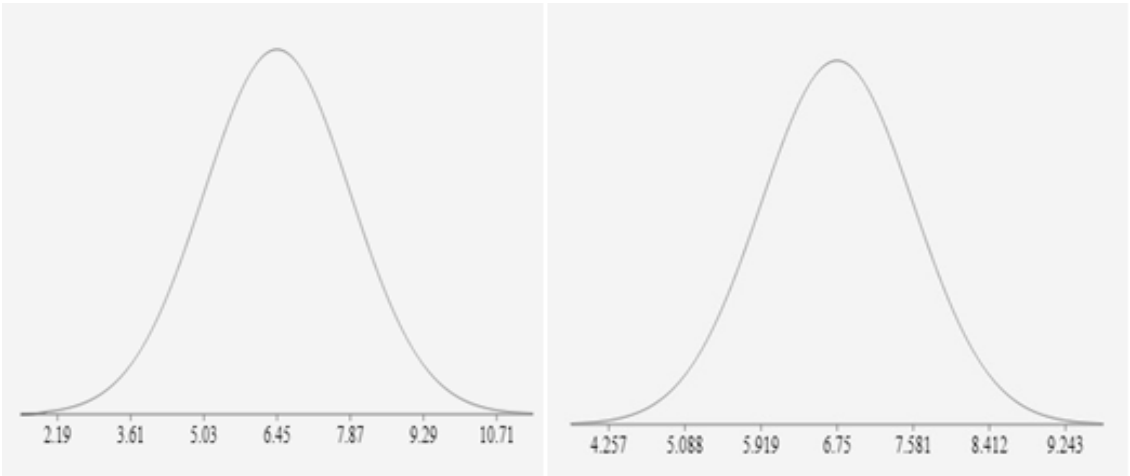

Figure No. 5: HBA1C Distribution in CRP<4 and CRP>=4

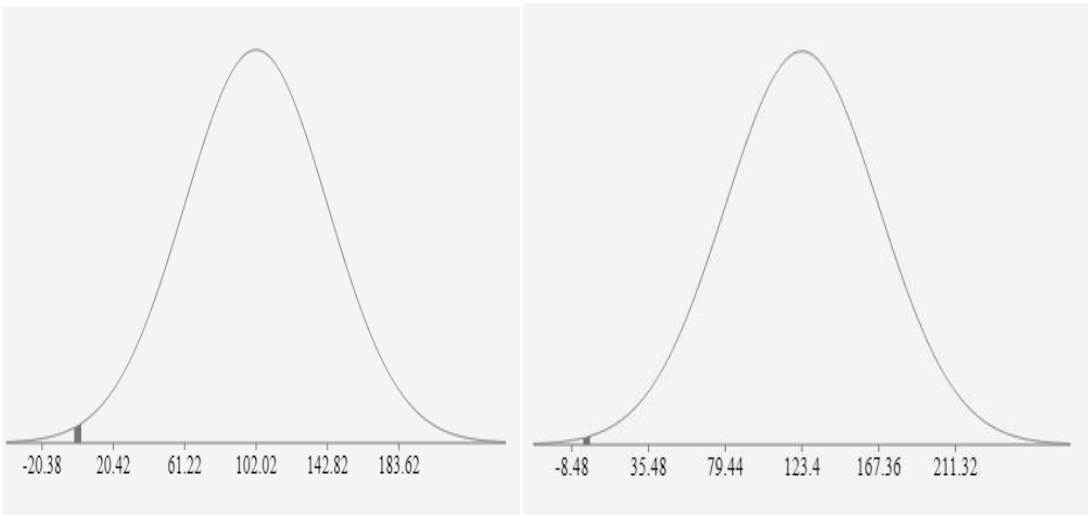

Figure No. 6: TG distribution in CRP<4 and CRP>=4

Figure No. 7: LDL distribution of CRP<4 and CRP>=4

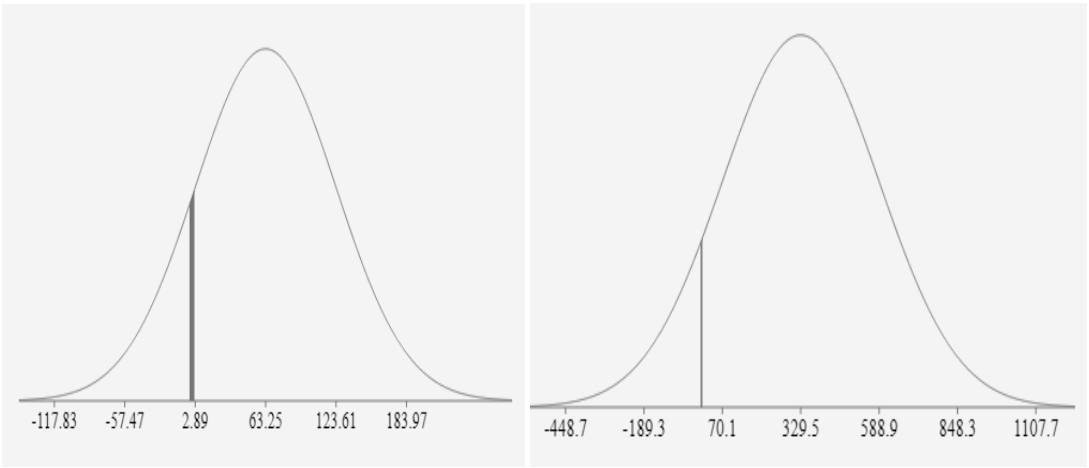

Figure No. 8: Spot urine ACR distribution in CRP<4 and CRP>=4

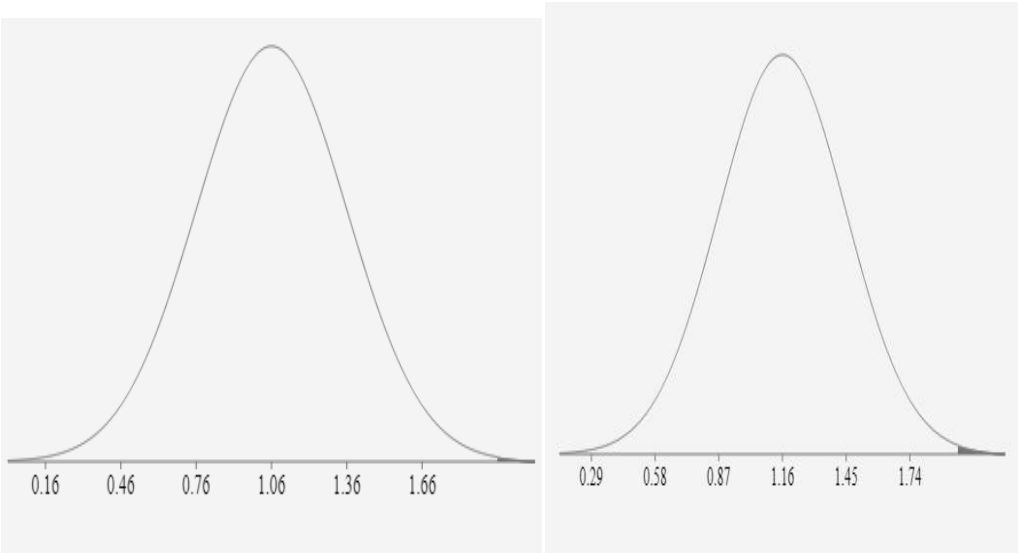

Figure No. 9: Serum Creatinine Distribution in CRP<4 and CRP>=4

TABLE No. 6: Characteristics of Diabetic nephropathy with respect to Proteinuria

	NORMOALBUMINURIA	MICROALBUMINURIA	MACROALBUMINURIA	P value
	(Spot urine ACR<30mg/gm)	(Spot urine ACR 30-300 mg/gm)	(Spot urine ACR >300mg/gm)	
	(n=17)	(n= 55)	(n=28)	
Age (years)	43.64± 4.91	48.69± 9.5	58±8.4	<0.05
BMI (kg/m2)	23.39± 6.82	22.96± 3.54	22.86± 1.56	0.9
Triglyceride (mg/dl)	110.4± 46.77	113.05± 48.97	123.25± 25.88	0.5
LDL (mg/dl)	84.05± 18.78	104.44± 30.75	123.78± 32.92	<0.05
HbA1C (%)	6.44± 1.06	6.66± 1.00	6.65± 0.67	0.6
Serum creatinine (mg/dl)	0.89± 0.2	1.15± 0.3	1.19± 0.2	<0.05
CRP(mg/l)	1.85±1.5	5± 5.09	9.17± 4.18	<0.05

Table No. 7: Relation between different Diabetic Proteinuria with respect to Age, LDL, Serum Creatinine and CRP

	AGE	LDL	SERUM CREATININE	CRP
Normo vs Microalbuminuria	P<0.05	P<0.05	P<0.05	P<0.05
Normo vs Macroalbuminuria	P<0.05	P<0.05	P<0.05	P<0.05
Micro vs Macroalbuminuria	P<0.05	P<0.05	**P>0.05**	P<0.05

Table 3 & Figure 1 are showing distributions of CRP among patients with proteinuria in our study population. Of 17 patients having normoalbuminuria, 16 patients were having normal CRP (94.12%). Of 28 patients having macroalbuminuria, all were having raised CRP (100%). However, raised CRP was found in 26 patients out of 55 patients having microalbuminuria (47.3%). (P<0.05).

Table 4 & Figure 2 are showing 26.3% of Stage 1 chronic kidney disease patients were having high CRP. 63% of Stage 2 chronic kidney disease patients were having high CRP. 63% of Stage 3 chronic kidney disease patients were having high CRP. (P<0.05) Association of eGFR with CRP was significant.

High CRP values were found in older people (P<0.05) and with higher triglyceride & LDL value (P<0.05). High CRP values were also found among patients with higher spot urine ACR (329.50±259.40 mg/gram) (P<0.05) and with higher creatinine values (P<0.05). However, CRP values did not correlate with BMI (P=0.5), HbA1C (P=0.2) (Table 5).

The clinical and biochemical characteristics of diabetic patients with proteinuria were represented in Table 6. Patient with macroalbuminuria (spot urine ACR >300 mg/gm) were older & having higher LDL and Serum creatinine and CRP values in comparison to patient with normal urine ACR (<30 mg/gm).

Proteinuria was significantly associated with age, serum creatinine, LDL and CRP values overall. But further post hoc analysis (Table 7) showed that age had no significant association

while comparing normoalbuminuria with microalbuminuria. The data comparing normoalbuminuria and microalbuminuria which were nearly age matched, HbA1c & triglyceride matched, significant rise of CRP was evident in microalbuminuric patients in comparison to normoalbuminuric patients. So CRP may have significant role in early stages of diabetic nephropathy.

DISCUSSION

Acute phase proteins are a class of proteins and their plasma concentrations increase or decrease in response to inflammations. Previous studies had demonstrated that inflammation played an important role in the pathogenesis of DM (Tsunoda, K., Arita, M., Yukawa, M., Ueyama, M., Furuta, M., Nakagawa, T., Nanjo, K. and Sanke, T., 2005; Kang, E.S., Kim, H.J., Ahn, C.W., Park, C.W., Cha, B.S., Lim, S.K., Kim, K.R. and Lee, H.C., 2005;Thorand, B., Löwel, H., Schneider, A., Kolb, H., Meisinger, C., Fröhlich, M. and Koenig, W., 2003)

CRP induces impaired self-regulation of glomerular pressure (GP) and dysfunction of glomerular endothelium (Moreno Ruiz I et al, 2011). So there is loss of albumin in urine through damaged glomeruli. These observations suggest that low-grade inflammation, reflected by high serum hs-CRP levels, may play a role in the induction of proteinuria(Yokoyama, H., Jensen, J.S., Myrup, B., Mathiesen, E.R., Rønn, B. and Deckert, T., 1996).

The study of Stehouwer CD et al in 2002 concluded that in type 2 diabetes, increased urinary albumin excretion, endothelial dysfunction, and chronic inflammation were interrelated processes that would develop in parallel & would progress with time(Stehouwer, C.D., Gall, M.A., Twisk, J.W., Knudsen, E., Emeis, J.J. and Parving, H.H., 2002.). Chronic inflammation as evidenced by high CRP was significantly associated with duration of diabetes mellitus according to Mojahediet al(Mojahedi, M.J., BONAKDARAN, S., Hami, M., SHEYKHIANI, M., Shakeri, M.T. and AYAT, E.H., 2009).

As proteinuria and CRP are the markers of systemic endothelial dysfunction and preclinical arterial inflammation as well (Mojahedi, M.J., BONAKDARAN, S., Hami, M., SHEYKHIANI, M., Shakeri, M.T. and AYAT, E.H., 2009; Torzewski, M., Rist, C., Mortensen, R.F., Zwaka, T.P., Bienek, M., Waltenberger, J., Koenig, W., Schmitz, G., Hombach, V. and Torzewski, J., 2000) they may have a role to develop other macrovascular complications including cardiovascular diseases (Pfützner, A., Schöndorf, T., Hanefeld, M.

and Forst, T., 2010). We had also studied serum triglyceride level and serum LDL level in association with CRP. Serum triglyceride is associated with atherosclerosis (Talayero, B.G. and Sacks, F.M., 2011.) and serum LDL is associated with coronary heart disease (Wilson, P.W., 1990) There were significant associations between CRP & serum triglycerides as well as between CRP and LDL in our study. Our findings were supported by Manoj Sigdelet al. 2014. However, Mojahedi, M.J., BONAKDARAN, S., Hami, M., SHEYKHIANI, M., Shakeri, M.T. and AYAT, E.H., 2009 found significant association of CRP with serum triglyceride only, not with LDL.

Few previous studies showed higher HbA1C was associated with higher CRP & they had significant association (Shelbaya, S., Amer, H., Seddik, S., Allah, A.A., Sabry, I.M., Mohamed, T. and El Mosely, M., 2012.). But we did not find any association between HbA1C and CRP possibly because of the presence of fairly controlled HbA1C in a tertiary hospital with proper follow up.

In some studies, they had found that there was a relationship between proteinuria and age (Navarro, J.F., Mora, C., Macıéa, M. and Garcıéa, J., 2003, Pannacciulli, N., Cantatore, F.P., Minenna, A., Bellacicco, M., Giorgino, R. and De Pergola, G., 2001, Gomes MB, Nogueira VG, 2004, Hansen, T.K., Gall, M.A., Tarnow, L., Thiel, S., Stehouwer, C.D., Schalkwijk, C.G., Parving, H.H. and Flyvbjerg, A., 2006) . We found similar result too. But there was also an association between CRP and age in our study. It might be the possibility that chronic inflammation, being a background process of diabetic nephropathy which in turn increased with advancement of age, was leading to rise in CRP. It was very well understood that the levels of hs-CRP were significantly associated with age and positively related to insulin resistance as concluded by Amanullah, S., Jarari, A. and Govindan, M., 2010. Besides Aronson et al. reported that CRP levels among middle-aged people were higher in those with Diabetes mellitus when compared with the healthysubjects (Shelbaya, S., Amer, H., Seddik, S., Allah, A.A., Sabry, I.M., Mohamed, T. and El Mosely, M., 2012).

We did not find any association of proteinuria or hs-CRP with body mass index similar to Mojahedi, M.J., BONAKDARAN, S., Hami, M., SHEYKHIANI, M., Shakeri, M.T. and AYAT, E.H., 2009. But it is opposing other studies, including Stehouwer, C.D., Gall, M.A., Twisk, J.W., Knudsen, E., Emeis, J.J. and Parving, H.H., 2002; Holm, J., Ravn, J. and Ingemann Hansen, S., 2006; Lee, W.Y., Park, J.S., Noh, S.Y., Rhee, E.J., Sung, K.C., Kim, B.S., Kang, J.H., Kim, S.W., Lee, M.H. and Park, J.R., 2004.

Serum creatinine in this study was also associated with proteinuria & CRP opposing the finding of Mojahedi, M.J., BONAKDARAN, S., Hami, M., SHEYKHIANI, M., Shakeri, M.T. and AYAT, E.H., 2009.

CONCLUSIONS

1. In our present study, we found that low grade inflammation as indicated by high CRP was an important predictor of diabetic nephropathy.

2. It was also found that advanced age in diabetics, dyslipidemia (higher triglycerides and LDL values), higher serum creatinine were also the major correlates with high CRP values.

3. Proteinuria is now widely accepted as an independent risk factor for cardiovascular morbidity and mortality (Currie, G. and Delles, C., 2014, Agrawal, V., Marinescu, V., Agarwal, M. and McCullough, P.A., 2009.) Thus measurement of CRP in diabetic nephropathy can also estimate the cardiovascular risks.

4. As our study population was from a tertiary hospital with fairly controlled HbA1C, we found no significant difference in HbA1C levels across proteinuria levels.

Limitations of the study

1. Small study population

2. A tertiary hospital based study

3. Study period was short.

4. Mostly lower income group & those belong to rural areas were represented in government hospital, so this study was not the true representative to society as a whole.

5. Few studies also demonstrated that antidiabetic drugs (Metformin/Pioglitazone) and statins might have effects to reduce inflammation (Chu, N.V., Kong, A.P., Kim, D.D., Armstrong, D., Baxi, S., Deutsch, R., Caulfield, M., Mudaliar, S.R., Reitz, R., Henry, R.R. and Reaven, P.D., 2002). We could not exclude the patients from our study whom were already on antidiabetic &/or Statin treatment.

6. This was a cross-sectional study. So we could not follow up the study population to assess the further consequences of inflammation and interventions.

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	***Author Name – Corresponding Author*** **- *Dr. Kaushik Mondal[1]** *Author Affiliation: MD student* [1]Calcutta National Medical College, Kolkata, West Bengal, India.
	***Author Name – Dattatreya Mukherjee[2]*** *Author Affiliation- MBBS student* *Author Address/Institute Address* - Jinan University, Guangzhou, P.R China.
	***Author Name – Debraj Mukhopadhyay[3]*** *Author Affiliation – Public health scholar* *Author Address/Institute Address*- Department of Public Health, School of Allied Health Sciences, Delhi Pharmaceutical Sciences and Research University (DPSRU), Govt. of NCT Delhi, New Delhi.