Association of novel inflammatory predictor serum C-reactive protein (CRP)/Albumin ratio with diabetic kidney disease in type 2 diabetes patients

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Abstract

Diabetic kidney disease (DKD) is one of the largest health problems globally and poses a potentially significant economic burden. Chronic inflammation in patients with type 2 diabetes mellitus(T2DM) is involved in the onset and development of DKD. In recent times, a novel inflammatory predictor, serum C-reactive protein (CRP)/albumin ratio has been studied in various inflammatory conditions. Since DKD is associated with chronic and low-grade inflammation, we aimed to analyze the levels of CRP/albumin ratio for the patients with type 2 Diabetic kidney disease (T2DKD) to those without DKD. A total of 176 diabetic patients were enrolled in the study, of which 81 were T2DKD and 95 were T2DM. The baseline demographic and clinical data including CRP/albumin ratio between the study groups were compared. Multivariate logistic regression analysis was used to analyze the independent risk factors of T2DKD and the receiver operating characteristic curve (ROC) was established to evaluate the predictive value of CRP/albumin ratio on T2DKD.

CRP/albumin ratio was found to be an independent risk factor for DKD (after adjustment to potential confounders such as BMI, Fasting blood glucose, HbA_1C and total cholesterol). The ROC analysis revealed that C-reactive protein/albumin ratio levels greater than 0.69 mg/g have 79 % sensitivity and 78% specificity in predicting DKD. Our results show that CRP/albumin ratio was elevated in type 2 diabetic patients with kidney disease. Thus, DKD is accompanied by elevated CRP levels, suggesting activation of inflammatory pathways in the progression of renovasculopathies.

Keywords: C-reactive protein to albumin ratio, Diabetic kidney disease, Inflammation.

Introduction

According to the recent reports of the tenth edition of the International Diabetes Federation (IDF), India is one of the top 10 countries across the world with the largest number of adults with diabetes[23]. Currently, 74.2 million in India have been affected by T2DM in 2021 and it is projected to be 124.9 million in 2045. Overall, 415 million people have been affected with T2DM globally and 5 million people deceased from diabetes-related complications[20].

Diabetic kidney disease (DKD) or Diabetic Nephropathy (DN) is one of the most devastating microvascular complications of diabetes mellitus and is the major cause of the end-stage renal disease (ESRD) worldwide[16]. DKD is characterized by a progressive deterioration in the glomerular filtration rate (GFR) and increased urinary albumin output that results in high morbidity and mortality[26]. During recent years, the involvement of tubular epithelial cells in the kidney in the pathogenesis of DKD has been emphasized as they release an increased quantity of inflammatory substances and fibrotic cytokine molecules following their activation[6].

The predominant culprits in this process are increased concentration of intracellular glucose and uncontrolled activation of receptors for advanced glycation end products (AGEs) that result in increased activity of transcription factor, nuclear factor-Kappa B (NF-κB) signaling cascade mechanism, the master regulator of the inflammatory process[24]. Presently to alleviate the benchmarks of DKD (i.e.) renal inflammation and albuminuria, the control of blood glucose and blood pressure represents the cornerstone of the treatment[30]. Despite their favorable outcomes, these attempts do not inevitably restrict the initiation and progression of micro and/or macrovascular complications of diabetes.

Existing evidences have indicated that several substances linked to inflammation such as urinary tumor necrosis factor (TNF-α), monocyte chemo-attractant protein-1 (MCP) chemokine and interleukin-8 (IL-8) are shown to be increased in patients with T2DKD[5]. Considering this, circulating inflammatory biomarkers might be satisfactory for the diagnosis and prediction of DKD[19] but the measurement of these molecules is quite expensive which limits their clinical applications. Among other inflammatory biological markers in plasma, C Reactive protein (CRP), an

acute phase protein is the most often used laboratory investigation for analyzing systemic inflammation in the initial phase.

In recent times, the role of novel inflammatory predictors has also been discussed in different inflammatory conditions. In view of this, C-reactive protein to serum albumin ratio has gained more popularity until recent times. CRP/albumin ratio is a synergy of biomarkers for systemic inflammation and dietary intake and it is recommended as a predictive marker for various inflammatory conditions such as Crohn's disease[29], Ulcerative colitis[4], Behcet's disease[12], enterocolitis in neonates[14], in patients on hemodialysis[9], acute pancreatitis[27] and even in hypertensive Covid 19 patients[7].

Since T2DKD was also related to increased inflammatory overburden, we postulated that CRP/albumin ratio levels could be associated with the development of DKD in patients with T2DM. Thus, we intended to compare CRP/albumin ratio levels and other biochemical variables of the T2DM subjects with DKD and without DKD.

Material and Methods

The current observational study was executed between November 2022 and July 2023 at Sri Ramakrishna Hospital, Coimbatore. The protocol of research was authorized and approved by the hospital ethical committee with reference number: R2019/411/CR/SRH/053. All the study subjects were briefed about the study procedures and they signed a consent form before blood collection. All measures followed were under the ethical standards of the corresponding committee on the experimentation of humans and with the Helsinki declaration of latest amendments, 2013. The inclusion criteria for group allocation were as follows: A total of 176 patients were recruited from the Diabetology and Nephrology clinics which comprised of 95 patients with type 2 Diabetes Mellitus (T2DM), 81 with type 2 Diabetic kidney disease(T2DKD). Based on the opinions of the specialists in the clinics, the study subjects were selected.

T2DM was defined by the criteria of the American Diabetes Association (ADA), 2012[2]. DM was defined by type 2 diabetic subjects with diabetes duration>10 years and urinary albumin/creatinine ratio (ACR) <30 mg/g. DKD was indicated by urinary albumin/creatinine ratio (UACR) ≥30 mg/g (measured by immunoturbidometric assay) in at least two of three fasting urine collections over 3 months or patients with ESRD under hemodialysis or kidney transplantation. The exclusion criteria were as follows: Patients with type 1 diabetes, diabetes duration less than 5 years, urinary tract infection, pregnancy, haematuria, autoimmune diseases, multiple co-morbidities, chronic inflammatory conditions and any other kind of kidney disease other than type 2 Diabetes Mellitus.

Clinical characteristics of subjects: Complete clinical examinations were done for all study subjects. All participants underwent demographic and anthropometric measurements. Using Omron Hem 8712, blood pressure (both systolic and diastolic) was measured after 10 min of rest. Mean arterial blood pressure (MAP) was determined using the equation: MAP= Diastolic BP +1/3(systolic BP-diastolic BP). From the measurements of weight and height, the body mass index (BMI) was calculated using kg/m^2. Urine and fasting blood samples were obtained from the subjects for biochemical analysis. The collection of blood samples was done a pre-dose to exclude the effect of the anti-diabetic drugs on biochemical results. After fasting in the early morning, 7 millilitres of venous blood were collected from each subject by venepuncture from the ante-cubital vein.

The blood was separated into 3 portions, 3 ml in ethylene diamine tetra acetic acid (EDTA) coated vial (for estimation of HbA_1C), 2 ml in fluoride vial (for estimation of fasting blood glucose) and 2 ml in plain vial (for preparation of serum). Routine lab investigations including blood glucose levels, kidney function tests and lipid indices were measured by fully automated analyzer VITROS® 7600/XT integrated systems. CRP/albumin ratio was calculated as CRP (mg/dl) divided by albumin (g/dl). The quantification of serum albumin was performed using the bromocresol green method and serum CRP was determined by non-competitive immunoassay.

Estimation of glycated haemoglobin (HbA_1C) was done by using a D-10™ 'BIO-RAD' high performance liquid chromatography (HPLC) and using related kits from Bio-Rad. These analytical procedures had been standardised with both internal and external quality control (EQAS) and performed routinely in the clinical laboratory of the hospital in the biochemistry department. Baseline residual renal function was assessed using the estimated glomerular filtration rate (eGFR) as determined by the creatinine equation provided by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula recommended by National Kidney Foundation (NKF)[10].

The CKD-EPI $eGFR = 141 \times \min(\text{Serum creatinine} \times 0.0113/k, 1)^{\alpha} \times \max(\text{Serum creatinine} \times 0.0113/k, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black]

where k is 0.7 for females and 0.9 for males, $^{\alpha}$ is -0.329 for females and -0.411 for males.

Statistical analysis: Data were entered in 2010 MS excel and analysed with the programme statistical package for social science version 25.0 (IBM SPSS Inc., statistics for windows). Data were presented as mean ± SD, median and inter quartile range, number and percentage (%) as appropriate. The data was checked for normality using Shapiro-Wilk test. Independent sample t test was used for normally distributed data whereas the Mann Whitney U test was used to compare quantitative variables that were not normally distributed. Pearson's correlation was done for

variables to find out the relation between parameters of inflammation. Receiver operating characteristic curve (ROC) was done according to the results. Multivariate logistic analysis was used to assess the relationship between inflammatory biomarkers and DKD. The null hypothesis was rejected at $P < 0.05$.

Results

Comparison of general clinical data between study groups: The baseline demographic characteristics and laboratory data of group I and group II are summarized in tables 1 and 2 respectively. Group I comprised of 35 women and 46 men while group II consisted of 42 women and 53 men (p=0.890). The average age of patients in group 1 was 59.3 ± 8.88, while that of patients in group 2 was 58.79 ± 7.90. There was no significant difference between the two groups (p=0.09). In addition, there was no significant difference in age of onset of diabetes, diastolic BP and smoking history.

The levels of BMI, systolic BP, MAP, duration of diabetes, fasting blood glucose and HbA_1C, in group I were higher than those in group II and the differences were statistically significant (P<0.001). Also, lipid indices which include total cholesterol, triglycerides, LDL and ARC were higher in group I when compared to group II (p<0.001) except HDL. The prevalence of retinopathy, a diabetes-related complication was higher among T2DKD patients compared to T2DM (p<0.001).

Besides, compared with T2DM, those with T2DKD has higher UACR [223.07(105.73-386.19)] mg/g vs 20.79(13.57-27.27) mg/g, p<0.001 and lower eGFR [36(21-40.50)] ml/min/1.73m^2 vs [88(66-118)] ml/min/1.73m^2, p<0.001 and lower albumin [3.6(3.2-4.0)] g/dl vs [4.2(4.0-4.5)] g/dl, p<0.001. Median CRP levels of group I and group II were 4.87(2.90-7.90) mg/dl and 1.98(1.0-2.9) mg/dl respectively (p<0.001). Median CRP/Albumin ratio levels of group I and II were 1.26(0.71-2.28)% and 0.50 (0.23-0.68)% respectively (p<0.001).

In Pearson correlation analysis, CRP/albumin ratio was found to be positively and significantly correlated with HbA_1C (r=0.46, p<0.001), CRP (r=0.41, p<0.001) and creatinine (r=0.97, p<0.001) respectively. However, CRP/Albumin ratio was negatively correlated with serum albumin (r=-0.3, p<0.001). Multivariate logistic regression analysis revealed that C-reactive protein/albumin ratio was an independent risk factor for diabetic nephropathy (after adjusted to BMI, fasting blood glucose, glycaemic control and total cholesterol). (Table 3)

Figure 1 shows the receiver operating curve (ROC) of the biochemical variables in determining diabetic kidney disease. The ROC analysis revealed that C-reactive protein/albumin ratio levels greater than 0.69 mg/g have 79 % sensitivity and 78% specificity in predicting DKD. (Table 4).

Discussion

DKD is the most severe vascular complication of Diabetes Mellitus and follows a very complex pathogenic process. Traditional risk factors for DKD include obesity, body mass index, dyslipidaemia, hypertension, smoking, physical inactivity and alcohol consumption. Additionally, novel risk factors like oxidative stress and inflammation, also increase the chance of DKD[13].

Albeit, urinary albumin is recognised as the earliest marker of DKD, significant glomerular damage might have occurred in advance when albumin starts to appear in urine. As albuminuria has certain limitations, the need for a more convenient serum biological marker with high sensitivity is required to diagnose DKD at the earliest during the developmental stage itself[1].

Table 1
Baseline characteristic of study subjects at the time of enrollment

Characteristics	Group I Type 2 Diabetic Kidney Disease (n=81)	Group II Type 2 Diabetes Mellitus (n=95)	p value	Inference
Demographic characteristics Male n(%)	46 (56.79%)	53 (55.79%)	0.890	Not significant
Female n(%)	35 (43.21 %)	42 (44.21%)		
Age (years)	59.3±8.88	58.79 ± 7.90	0.097	Not significant
Clinical characteristics: Body Mass Index (BMI)(kg/m^2)	25.0 ± 4.15	23.32 ± 3.73	0.005	Significant
Systolic BP (mm/Hg)	136.79 ± 9.82	120.08 ± 7.07	<0.001	Highly significant
Diastolic BP(mm/Hg)	82.27 ± 5.58	81.05 ± 6.56	0.193	Not significant
Mean Arterial Pressure (MAP) (mm/Hg)	100.16 ± 5.57	94.06 ± 6.36	<0.001	Highly significant
Age of onset (years)	48.08 ± 6.83	47.36 ± 6.40	0.508	Not significant
Diabetes duration (years)	14.90 ± 3.06	11.85 ± 3.99	<0.001	Highly significant

n- number of participants; Categorical data are represented as numbers (%); continuous data as mean ± SD.

Table 2
Laboratory results of the study groups

Variables	Group I	Group II	p value	Inference
Glycemic status: Fasting blood glucose(mg/dl)	183.78 ± 33.15	141.84 ± 29.43	<0.001	Highly significant
Post-prandial blood glucose (mg/dl)	251.36 ± 60.58	202.31 ± 42.25	<0.001	Highly significant
HbA_1C(%)	9.42 ± 2.66	7.49 ± 1.07	<0.001	Highly significant
Diabetic complications Kidney profile: Creatinine (mg/dl) [ł]	1.8(1.4-2.5)	0.8(0.6-0.9)	<0.001	Highly significant
e GFR -CKD-EPI (ml/min) [ł]	36(21-40.50)	88(66-118)	<0.001	Highly significant
UACR (mg/g) [ł]	223.07(105.73-386.19)	20.79 (13.57-27.27)	<0.001	Highly significant
Lipid profile: Total cholesterol (mg/dl)	309.99 ± 54.12	183.85 ± 44.12	<0.001	Highly significant
Triglycerides (mg/dl)	255.53 ± 50.90	174.67 ± 45.84	<0.001	Highly significant
HDL (mg/dl)	35.19 ± 7.42	36.05 ± 6.82	0.836	Not significant
LDL (mg/dl)	211.44 ± 51.45	113.9 ± 32.05	<0.001	Highly significant
ARC (TC/HDL ratio)	7.02 ± 1.68	5.17 ± 1.24	<0.001	Highly significant
Inflammatory markers CRP (mg/dl)[ł]	4.87(2.90-7.90)	1.98(1.0-2.9)	<0.001	Highly significant
Albumin (g/dl) [ł]	3.6(3.2-4.0)	4.2(4.0-4.5)	<0.001	Highly significant
CRP/albumin ratio (mg/g)[ł]	1.26(0.71-2.28)	0.50(0.23-0.68)	<0.001	Highly significant
Retinopathy n (%)	73(90.12%)	30(31.57%)	<0.001	Highly significant
Smoking (n %)	11(12.9%)	17(17.89%)	0.836	Not significant

Unless indicated otherwise, data represented as mean ± SD; [ł]continuous data shown as median with corresponding 25th and 75th (IQR); eGFR- Estimated Glomerular Filtration Rate using chronic kidney disease epidemiology collaboration equation; UACR – urine albumin creatinine ratio; HbA_1C: NGSP; National GlycoHaemoglobin Standardization Program; ARC- Atherogenic ratio of cholesterol; CRP-C-reactive protein

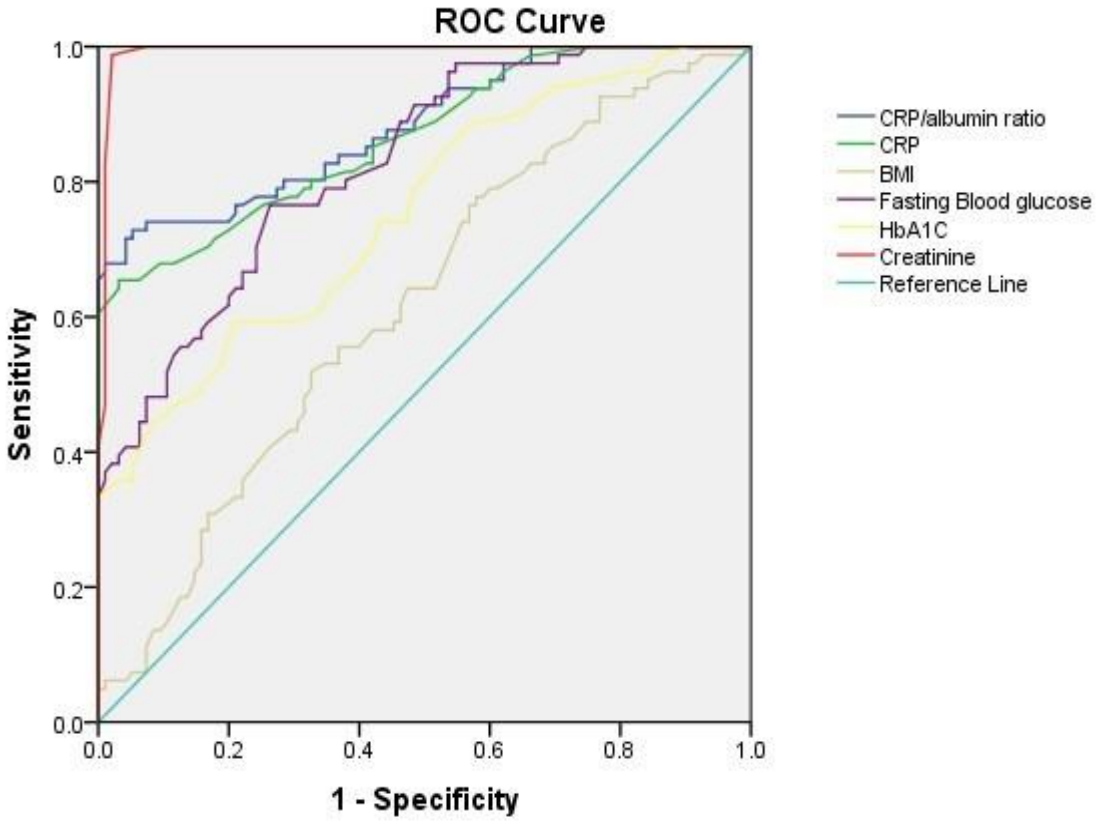

Fig. 1: Area under the receiver operating characteristics (AUROC) curves showing association of different variables with diabetic kidney disease

Table 3
Logistic regression analysis of the study variables in predicting DKD

Factors	Crude odds ratio (95%CI)	p value	Adjusted odds ratio (95%CI)	p value
BMI	0.896(0.827-0.971)	0.007	1.01(0.842-1.216)	0.903
HbA_1C	0.494(0.377-0.647)	<0.001	2.51(1.271-4.521)	0.007
Fasting blood glucose	0.955(0.942-0.969)	<0.001	0.958(0.926-0.991)	0.014
Total cholesterol	0.954(0.942-0.967)	<0.001	0.955(0.937-0.974)	<0.001
C-reactive protein/albumin ratio	0.011(0.003-0.052)	<0.001	0.359(0.255-0.505)	<0.001

(CI-confidence interval)

Table 4
ROC curve analysis in predicting disease in T2DKD

Variables	AUROC	p value	95%CI	Cut off	Sensitivity	Specificity
CRP/Albumin ratio	0.88	<0.001	0.83-0.93	0.69	79%	78%
CRP	0.86	<0.001	0.81-0.91	2.85	76 %	78 %
BMI	0.62	0.007	0.54-0.70	25.08	43 %	71 %
Fasting blood glucose	0.83	<0.001	0.76-0.88	148.5	76%	75%
HbA_1C	0.80	<0.001	0.68-0.82	8.4	60 %	80 %
Creatinine	0.89	<0.001	0.87-1.00	1.1	97%	80 %

In the early progressive phase of DKD, macrophages accumulate in the renal cells and release cell adhesion substances, proinflammatory cytokines and chemokines, which recruit more macrophages in the kidney and aggravate the inflammatory burden. CRP, being commonly categorized as a marker of inflammation is radically available and comparatively more economical than other expensive inflammatory markers and therefore, it can provide valuable information in the terms of inflammatory status of the disease condition and its prognosis. Usually, CRP is an acute phase reactant synthesized mainly by the liver in response to the stimuli of interleukin-6 (IL-6). Along with other acute phase reactants like TNF-α and IL-6[5], CRP levels in plasma increase throughout sustaining inflammation. Elevated CRP levels have also been associated with increased morbidity and/or death in both pre-dialysis[17] and haemodialysis patients[28].

Clear fact is not still known that the CRP is solely a biological marker of ongoing inflammatory status or a predominant role in the vascular disease process. The latest findings in the literature focussed on the association between CRP/albumin ratio and inflammatory burden which aids to improve the diagnostic accuracy and prognostic predictions when compared to CRP alone. In the present study, we found that elevated CRP/Albumin ratio levels in T2DKD could predict DKD in patients with type 2 diabetes mellitus.

In our study, the median CRP levels of group I increased significantly when compared to group II. This is in concordance with Guo et al[8] who reported increased erythrocyte sedimentation rate (ESR) and high sensitive CRP(hs-CRP) levels in patients with DKD compared to those without DKD. The study of Stehouwer et al[22] concluded that both the increase in albumin excretion, endothelial dysfunction and exuberated inflammation were interrelated processes that would develop in parallel and would progress over time in T2DM. Chronic inflammation as evidenced by high CRP was significantly associated with the duration of diabetes in our study in agreement with the findings of Mojahedi et al[15] who found a significant association with disease duration.

The relationship between DKD and the duration of diabetes is explained by the fact that prolonged exposure to hyperglycemia causes damage to the glomerulus, tubule-interstitium and vasculature either directly or through hemodynamic changes. As proteinuria and CRP are the markers of systemic endothelial dysfunction and preclinical arterial inflammation as well[25], they may have a role to develop other macrovascular complications including cardiovascular diseases[18]. There was a significant association not only in CRP and dyslipidemia but also between CRP/albumin ratio and serum triglycerides as well as between CRP/albumin ratio and LDL in our study. Our findings were supported by Sigdel et al[21] who found the significant increase in lipid indices. However, Mojahedi et al[15] a found significant association of CRP with serum triglycerides only and not with LDL.

We have noticed that median CRP/Albumin ratio levels of group 1 significantly increased when compared to group II. This is in concordance with Bilgin et al[3] who observed the association of CRP/albumin ratio with diabetic nephropathy in type 2 diabetes mellitus and reported that one unit (0.1%) elevation in CRP/albumin ratio increased the risk of nephropathy by 3.5 folds (p<0.001, 95%CI: 2.24-5.45).

A positive association between CRP/albumin ratio and serum creatinine was also noted in our study. Mounting

evidence suggests that a declining glomerular filtration rate, as reflected by increasing serum creatinine, may be accompanied by increasing levels of inflammation. The etiology of inflammation is not completely understood but could be related to the accumulation of proinflammatory compounds such as cytokines (TNF-α) or advanced glycation end products[11].

Nevertheless, inflammatory overburden, highly infectious state and poor nutritional status may cause drastic changes in CRP and marked decrease in level of albumin. Therefore, these conditions should be taken into account before considering as a biomarker of DKD. Our findings underline the possible association of CRP/albumin ratio and T2DN and it offers a resource for further studies. Further investigations with greater samples are encouraged to elucidate the role of CRP/albumin ratio to predict DKD in patients with type 2 diabetes mellitus.

Conclusion

CRP is a simple, effective outcome predictive biomarker that yields reproducible results in inflammatory conditions. The sensitivity and accuracy to predict DKD are increased by taking albumin into account. Therefore, readily available cost-effective parameter, CRP/albumin ratio should be added to stratify the risk in patients suffering from DKD.

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