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TO EVALUATE, CRP AS A MARKER FOR CARDIOVASCULAR RISK

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Abstract

Background: Persistent, low-grade inflammation likely participates in the pathophysiology of both atherosclerosis and kidney disease. Although high-sensitivity C-reactive protein (hsCRP) predicts future cardiovascular risk and chronic kidney disease (CKD), it is unknown whether hsCRP levels predict adverse renal outcomes in patients with cardiovascular disease.

Methods: We included All inpatients with clinical and / or biochemical evidence of chronic kidney disease, admitted in the hospital for CKD and cardiovascular disease. Patients who refused to give consent, Critically/terminally ill Patients, Patients with pre-existing cardiac valvular disease, HIV Positive Patients, Patients taking immune-suppressive therapy, Patients on chemo-therapy, Acute kidney injury patient were excluded. After taking institutional ethical clearance and written consent from the patients a cross sectional observational study was conducted on patients admitted in the hospital, who had clinical and / or biochemical evidence of chronic kidney disease. A detailed thorough history was taken, general physical examination, systemic examination and routine and specific lab investigations were done to find out the underlying aetiology, clinical features and outcome of chronic kidney disease. Pro forma I -Informed consent form ANNEXURE G-Master Chart Proforma.

All the data analysis was performed using IBM SPSS ver. 20 software. Frequency distribution and cross tabulation was used to prepare the tables. Quantitative variables were expressed as the mean and standard deviation. Categorical data was expressed as percentage. Categorical variables were compared by chi-square test. Mean was compared using one way ANOVA analysis. PRISM and Microsoft office was used to prepare the graphs. HsCRP tests measured during hospitalization/emergency room visits.

Results: This prospective observational study was done in 100 patients in central India, to observe CRP levels in CKD Patients and to evaluate CRP as a marker for Cardiovascular risk, From 1st December 2019 to 31th October 2020.

In this study group majority of the patients were above 30 years of age. The mean age of the study was 47.8 years, male: female incidence was in the ratio of 1.85:1. There was significant predominance of CKD in male patients in the study. Patterns in the incidence of kidney disease across gender were generally consistent, with higher rates occurring in men than in women. Similarly, men were reported to have greater rates of progression of nondiabetic CKD for some specific types of kidney disease, especially compared with premenopausal women.

In our study SBP and DBP were raised above the reference levels, mean SBP were 148.2±8.81 and mean DBP were 99±6.89. The mean level of urea was 146.6±27.5 mg/dl. A significant correlation between serum creatinine and CRP levels were noted, which has been shown by significant p- value of <0.0001 and a significant negative correlation between CRP levels and eGFR has also been noted , which has been shown by significant p-value of <0.0001. There was an insignificant negative correlation between serum creatinine levels and haemoglobin levels, which has been shown by insignificant p-value of >0.05 [mean level of creatinine was 11.6±2.7 mg/dl, mean haemoglobin was 7.469±0.80 mg/dl, hsCRP was raised above reference level, The mean level hsCRP was 5.45±2.79 mg/dl].

The average eGFR was 5.45±2.79 ml/min/1.73m2. Most of patients were ESRD patients and were in stage 5 of CKD, with most common associated disease being HTN (49%) followed by DM (26%), whereas CKD alone were 36%. In most of the patients hsCRP was raised above the baseline. The mean levels of hsCRP were 5.45±2.79 mg /dL. In 85% of patients hsCRP was raised above 5 mg/dL and in 45 % of subjects, hsCRP was >5 mg/dL.

Conclusions: The present study shows excess inflammation and oxidative stress in the CKD patients, as hsCRP were raised in 45% of patients above 5 mg/dL which is similar to the previous studies. Renal insufficiency causes a prolonged acute phase inflammatory reaction that is accompanied with elevated inflammatory markers such as hsCRP, IL-6. These inflammatory markers are significantly associated with cardiovascular morbidity and mortality. Elevated hsCRP was associated with subsequent risk of AKI and progression of CKD, irrespective of baseline kidney function.

INTRODUCTION

Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiologic processes associated with abnormal kidney function, and a progressive decline in glomerular filtration rate (GFR). The term CRF applies to the process of continuing significant irreversible reduction in nephron number, and typically corresponds to CKD stages 3–5 [1].

The uremic milieu of CKD patients contains high amounts of proinflammatory proteins and cytokines like C reactive protein, interleukin -6 and others[7]. Atherosclerosis too is an inflammatory condition of the arteries and CRP which is produced chiefly in the hepatocytes under the influence of interleukin 6 (IL-6) and IL-1 is an important inflammatory mediator [3].

There are studies to demonstrate the role of increased levels of CRP and reactive oxygen species in ESRD and patients undergoing dialysis. The study was intended to determine the levels of high sensitivity C reactive protein (hsCRP) as a marker of inflammation in pre-dialytic renal disease patients and to decipher if there is any association between serum hsCRP and MDA levels with the progression of kidney disease [3]. Certain immunological tests might help to make sure the level of inflammation including a variety of cytokine levels and acute phase proteins, of which c-reactive protein is very central and sensitive.

Occurrence of an inflammatory response, old age and extent of hydration could also be grounds for hypoalbuminemia. There is a considerable association between serum albumin and CRP levels in CKD children, as CRP levels boost up there is a reduction in serum albumin, the reason being pro-inflammatory cytokines such as IL-1, IL-6 and TNFα. These cytokines cause an increase in positive APRs in liver but they also cause reduction in synthesis of albumin and other negative APRS [7]. So, whenever the levels of one are increasing in inflammation such as CKD the other goes on decreasing and vice versa [8].

hsCRP was discovered in 1930 by William Tillett and Thomas Francis, investigators at the Rockefeller University. They found it could be isolated from the blood of patients with a specific type of pneumonia. This increment is due to a rise in the plasma concentration of IL-6 which is produced mainly by macrophages and adipocytes. hsCRP has been introduced as a predictor of cardiovascular events in cardiovascular medicine [15]. It has been noted that hsCRP binds to damaged endothelial cells, activates the complement system, promotes foam cell formation, aggregates low-density lipoprotein, and stimulates tissue factor production by monocytes.

CKD is a chronic inflammatory state caused by both patient and dialysis related factors like- uremic milieu, infection, oxidative stress, co-morbidities, obesity, genetic or immunologic factors, exposure to dialyzer membrane and dialysate [17]. Consequences of chronic inflammation in CKD patients include malnutrition, anaemia, hypo-responsiveness to erythropoietin, CVD and increased mortality. Amuk *et al* reported that CRP and endothelial function could provide complementary prognostic information regarding future cardiovascular disorders in renal patients [18]. However, patients whose hs-CRP levels remain elevated overtime would be expected to have greater mortality than patients with occasionally elevated levels.

Therefore, much interest has been focused on inflammation, the ―secret killer in ESRD that promotes atherosclerosis, malnutrition, and anaemia in this group of patients. The new clinical meaning of hs-CRP in ESRD patients is that of an index that reflects their overall health state as determined by several conditions. A high value indicates an unfavourable condition aggravated by renal insufficiency and its complications, while a lower one should show a relatively good condition of their health. [21]

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AIMS AND OBJECTIVES
This prospective observational study was conducted in 100 patients in NSCB Jabalpur medical college with following aims
-to observe CRP level in CKD Patients.
- to evaluate, CRP as a marker for Cardiovascular risk.
From 1st December 2019 to 31th October 2020

INCLUSION CRITERIA–
All inpatients with clinical and / or biochemical evidence of chronic kidney disease

EXCLUSION CRITERIA
1) Patients who refused to give consent.
2) Critically/terminally ill Patients
3) Patients with pre-existing cardiac valvular disease.
4)HIV Positive Patients.
5) Patients taking immune-suppressive therapy.
6) Patients on chemo-therapy.
7) Acute kidney injury patients.

METHODOLOGY- After taking institutional ethical clearance and written consent from the patients a cross sectional observational study was conducted on patients admitted in the hospital, who had clinical and / or biochemical evidence of chronic kidney disease. A detailed thorough history was taking, general physical examination, systemic examination and routine and specific lab investigations were done to find out the underlying aetiology, clinical features and 65 outcomes of chronic kidney disease.
Pro forma I -Informed consent form ANNEXURE G-Master Chart Proforma

Statistical analyses:
All the data analysis was performed using IBM SPSS ver. 20 software. Frequency distribution and cross tabulation was used to prepare the tables. Quantitative variables were expressed as the mean and standard deviation. Categorical data was expressed as percentage. Categorical variables were compared by chi-square test. Mean was compared using one way ANOVA analysis. PRISM and Microsoft office was used to prepare the graphs.

Observations and results
We observed that-

TABLE NO-1

AGE	MALE	FEMALE	TOTAL	P-VALUE
21-30	11 [16.9%]	7 [20%]	18 [18%]	
31-40	8 [12.3%]	4 [11.4%]	12 [12%]	
41-50	17 [26.2%]	13 [37.1%]	30 [30%]	0.004
51-60	8 [12.3%]	10 [28.6%]	18 [18%]	
ABOVE 60	21 [32.3%]	1 [2.9%]	22 [22%]	
TOTAL	65 [100%]	35 [100%]	100 [100%]	

-In this study group majority of the patients were above 30 years of age. Mean age of the study was 47.8 years.
-Male: female ratio of 1.85:1. There was significant predominance for CKD in male patients in study.

Parameter	N	Minimum	Maximum	Mean	Std. deviation
Age	100	21	74	47.89	14.24
SBP	100	130	160	148.2	8.81
DBP	100	80	110	99	6.89
Blood urea	100	85	230	146.6	27.55

-In our study SBP and DBP were raised above the reference levels.
- mean SBP was 148.2±8.81 and mean DBP was 99±6.89.
- in our study urea was raised above reference level. The mean level of urea was 146.6±27.5 mg/dl.

Pearson correlation

Parameter 1	Parameter 2	R- value	P- value
CRP	eGFR	-0.454	<0.0001
CRP	S. creatinine	0.490	<0.0001
Haemoglobine	S. creatinine	-0.132	0.190

-As shown in the table there is a significant correlation between serum creatinine levels and CRP, which is shown by significant p- value of <0.0001.
-there is a significant negative correlation between CRP levels and eGFR, which is shown by significant p-value of <0.0001.
- there is an insignificant negative correlation between serum creatinine levels and haemoglobin, which is shown by insignificant p-value of >0.05.

Parameter	N	Minimum	Maximum	Mean	Std. deviation
S. creatinine	100	4.4	18.7	11.61	2.77
Haemoglobin	100	6.1	11	7.469	0.80
CRP	100	0.7	15.23	5.454	2.79
eGFR	100	2	13	5.42	2.22

- In our study creatinine was raised above reference level. The mean level of creatinine was 11.6±2.7 mg/dl.
- The mean haemoglobin was 7.469±0.80 mg/dl.
- In our study hsCRP was raised above reference level. The mean level was 5.45±2.79 mg/dl.
- The average eGFR was 5.45±2.79 ml/min/1.73m2. Most of patients were ESRD patients and were in stage 5 of CKD.

Diagnosis	Frequency	Percentage
CKD With ALD With HTN	1	1
CKD With HTN With CLD	4	4
CKD	34	34
CKD with ALD	2	2
CKD With Anemia	2	2
CKD with CLD	4	4
CKD with hepatitis C	1	1
CKD with HTN	18	18
CKD With HTN CLD	1	1
CKD With HTN With ALD	5	5
CKD with HTN With T2dm	5	5
CKD With HTN with T2dm with CLD	2	2
CKD With MI	1	1
CKD with T2dm	9	9
CKD With T2dm with Anemia	1	1
CKD With T2dm With HTN	6	6
CKD with dm With HTN With Anemia	3	3
CKD With T2dm with Anemia	1	1

CKD With T2dm With HTN	6	6
CKD with dm With HTN With Anaemia	3	3
Total	100	100

-This table represents various other disease associated with CKD in the current study.
-Most commonly associated disease being HTN(49%) followed by DM(26%), CKD alone being 36%.
-The study enrolled 100 subjects out of which 65 were male and 35 were female.
-In most of the patients hsCRP was raised above the baseline. The mean levels of hsCRP were 5.45±2.79 mg /dL. In 85% of patients hsCRP was raised above 5 mg/dL and in 45 % of subjects, hsCRP was >5 mg/dL.
-The mean haemoglobin level in our patients was 7.469 ± 0.80 mg/dL.
-The mean eGFR in our subjects was 5.42±2.21 mL/min/1.73m2.
-The mean SBP in our patients was 148±8.81.
-The mean DBP in our patients was 99±6.89.
-8 Patients (8.0%) had heart failure.
-2 (2.0%) patients had CVA.
-3(3.0%) patients had CAD.
-16(16.0%) patients were found to have retinopathy on examinations.
-None of the patients had neuropathy clinically.
-In the study correlation between heart failure and levels of hsCRP was not significant. (_t,, value =0.83, df=3,p value= 0.994).
-In our study correlation between CVA and levels of hsCRP was not significant.(t,, value=2.497, df=3,p value= 0.476).
-In our study correlation between CAD and levels of hsCRP was not significant. (t,,value=4.145, df=3,p value= 0.246)
The present study shows excess inflammation and oxidative stress in the CKD patients, as hsCRP were raised in 45% of patients above 5 mg/dL which is similar to the previous studies. Renal insufficiency causes a prolonged acute phase inflammatory reaction that is accompanied with elevated inflammatory markers such as hsCRP, IL-6.
These inflammatory markers are significantly associated with cardiovascular morbidity and mortality. The subjects in our study were anaemic (Hb=7.46±0.80 gm/dL).

DISCUSSION-
The present study shows excess inflammation and oxidative stress in the CKD patients, as hsCRP were raised in 85% of patients hsCRP was raised above 3 mg/dL.

Our study enrolled 100 patients, of which 35were females and 65 were male. Patterns in the incidence of kidney disease across gender were generally consistent, with higher rates occurring in men than in women. Similarly, men were reported to have greater rates of progression of nondiabetic CKD for some specific types of kidney disease, especially compared with premenopausal women. US Renal Data System has also reported the incidence rates for end-stage renal disease (ESRD) approximately 60% higher among men than among women. The prevalence of CKD increases with age and is reported to be as high as 56% in people aged 75 years or older [26].

Longitudinal studies of subjects without kidney disease have demonstrated a decline in GFR with increasing age in some but not all subjects, which implies that nephron loss may be regarded as part of normal aging. On the other hand, aging is associated with an increase in several other risk factors for CKD - including hypertension, obesity, and cardiovascular disease - that may contribute to the rise in prevalence of CKD. in our study we included patients of age between 21 to 74 years mean age is 47.

The mean haemoglobin level in our patients was 7.469 ± 0.801 mg/dL. The prevalence of anaemia in patients with CKD has been widely studied. In general, anaemia becomes more frequent as renal function declines, becoming almost universal in end-stage renal disease (ESRD). Astor and colleagues studied the NHANES III including 15,419 participants 20 years and older. Anemia (World Health Organization definition, Hgb 5 mg/dL. In previous studies also it was found to be raised in patients of chronic kidney disease.

EL-Attar HA *et al* [24] found increase in hsCRP in patients on haemodialysis therapy when compared to both controls and patients on non-dialytic therapy.

Dr. Sumanth kumar and colleague [51] found the levels of hsCRP were high in patients with chronic kidney disease as compared to the controls. The mean and standard deviation (SD) of hsCRP in the total cases was 26.08 ±5.73, as compared to the control group which was 0.83±0.15. Sanjin racki *et al* [45] in their study had 65.5% patients with hsCRP> 3mg/dL, in which 111 (47.9%) patients had hsCRP >10.0 mg/L. A study by Fred S. Apple [17] had found elevated hsCRP in 46% of the patients. Zimmermann J *et al* [38] found Serum CRP elevated (more than 8) in 46% of subjects.In a study by stenvinkel P *et al* [2] 32% of all patients had elevated CRP levels.

Traditionally, hsCRP has been regarded as a predictor of future risk for heart attack, stroke, sudden cardiac death, and the development of peripheral arterial disease. AHA demonstrates that levels of CRP less than 1, 1-3, and greater than 3 mg/L discriminate between individuals with low, moderate, and high risk for future cardiovascular event. Renal insufficiency causes a prolonged acute phase inflammatory reaction that is accompanied with elevated inflammatory markers such as hs-CRP, IL-6, albumin and fibrinogen. These inflammatory markers are significantly associated with cardiovascular morbidity and mortality.

The potential mechanisms responsible for the association of inflammation with renal function decline are not clear. In vitro experiments showed that CRP reduced the release of basal and stimulated nitric oxide and might lead to oxidative stress which might be related to renal function decline. In addition, high circulating CRP levels might induce injuries through deposition in the glomerular endothelium and reduce functional renal mass, and contribute to renal scaring, interstitial fibrosis, and tubular hypertrophy through several hypothesized mechanism, such as increased angiotensin II levels and elevated transforming growth factor-b levels.

The average eGFR in our patients was 5.45± 2.79 mL/min/1.73m2. Most of the patient were ESRD patients and were in STAGE V of CKD. In previous studies there was association between the cardiovascular events and raised hsCRP levels.

In the study by Diana Jalal *et al* [26], 61 after 4 years of follow-up, 204 (6.4%) participants experienced a major cardiovascular event. High hs-CRP levels and CKD at baseline were associated with a greater risk of vascular events. Compared to patients with low hs-CRP/non-CKD, the adjusted HR (95% CI) for vascular events was 1.93 (1.45; 2.89) for high hsCRP/CKD.

Zimmermann J *et al* [14] followed patients of CKD for 2 years. During the follow-up, 72 patients (25.7%) died, mostly due to cardiovascular events (58%). Overall mortality and cardiovascular mortality were significantly higher in patients with elevated CRP (31% vs. 16%, $P < 0.0001$, and 23% vs. 5%, $P < 0.0001$, respectively).

Yeun JY et [13] al followed haemodialysis (HD) patients during a 34-month follow-up period and found that the group with the greatest CRP level (>11.5 microg/mL) had the lowest survival.

Patients with end stage renal disease (ESRD) have higher than expected mortality which can not only be explained by traditional risk factors of atherosclerosis like diabetes, hypertension, dyslipidaemia but also by factors like inflammation, malnutrition, and predisposition to infection. These factors are also believed to have substantial contribution in the development of cardiovascular diseases as well as morbidity and mortality. The association between inflammatory markers and cardiovascular events, coronary artery disease and its complications occur with high frequency in patients with ESRD; and substantially contributes to cardiovascular morbidity and mortality in this population. However, serum CRP elevation is not specific as it may change due to several inflammatory or non-inflammatory responses.

In our study a significant association may have been missed due to sample size in the present study. Similarly, an association between the levels of oxidant stress biomarkers and cardiovascular disease may have been

missed due to sample size. The demerit of the present study is that it is a cross sectional, observational study and has relatively small sample size.

SUMMARY & CONCLUSION

This cross-sectional, observational study was carried out to assess the highly sensitive c-reactive protein (hsCRP) levels in chronic kidney disease. 100 patients were enrolled who fulfilled the inclusion criteria. Questionnaires were administered to the study subjects by the researchers to obtain demographic information such as age, gender and clinical history such as history of renal symptoms, common etiologies such as hypertension, diabetes mellitus, retroviral disease, haemoglobinopathy, obstructive uropathy, connective tissue disease and previous or family history of renal disease. Study subjects were physically examined. Weight was measured using a weighing scale with subjects wearing light clothing.

The etiology of renal disease in CKD subjects were determined by the researchers using the information obtained from administered questionnaires, physical examination findings and investigations. Micro-vascular complications were defined as neuropathy, retinopathy and macro-vascular complications were defined as heart failure, coronary artery disease, cerebrovascular disease. Blood sampling was performed between 8 and 10 a.m. after an overnight fasting. Laboratory parameters included CBC, kidney function tests, fasting glucose, lipid profile, and serum highly sensitive C - reactive protein. GFR was calculated by the Cockcroft Gault equation.

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