Short communication

Novel biomarkers of inflammation for endothelial dysfunction in chronic kidney disease patients

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ABSTRACT

Introduction and Aim: One of the main complications of chronic kidney diseases (CKD) resulting in morbidity and mortality is cardiac complications. High-sensitive C -reactive protein (hs- CRP), a novel biomarker of systemic inflammation is elevated in all the stages of kidney impairment. This leads to endothelial dysfunction resulting in cardiovascular complications. The aim is to evaluate the levels of novel inflammatory biomarkers for endothelial dysfunction which could predict cardiovascular risk in CKD patients.

Materials and Methods: This cross-sectional study was conducted among 50 CKD patients at a tertiary care hospital in Chennai. Study participants were from both sexes, aged between 20 and 65 years. Fasting blood samples were drawn for analysis of lipid profile, hs- CRP, calcium and phosphorus.

Results: The participants were grouped into three based on the hs-CRP Levels, as Low (<0.80 mg/L), Medium (0.81–1.76 mg/L) and High (>1.76 mg/L). Serum creatinine was significantly increased (P=0.007) across the groups. hs-CRP showed positive correlation with creatinine, while it showed negative correlation with HDLc.
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Conclusion: Highly sensitive CRP is a marker of endothelial dysfunction. Elevated hsCRP levels in CKD patients indicate that they are prone for cardiovascular complications. Early detection of systemic low-grade inflammation may prevent future cardiovascular complications.

Keywords: Chronic kidney disease; inflammation; endothelial dysfunction; high- sensitive C-reactive protein; cardiovascular risk.

INTRODUCTION

Chronic kidney disease (CKD) is a global health burden which is prevalent in both developed and developing countries. CKD from the early to the late stages is strongly associated with cardiovascular (CV) events which increase morbidity and mortality by several folds in CKD patients (1). Recently lot of studies have shown that even mild renal impairment could lead to endothelial dysfunction. This could precipitate CV events leading to premature death even in the early stages of CKD patients. The traditional risk factors for CV events in CKD patients are diabetes mellitus, hypertension, smoking, hypercholesterolemia, age and non-traditional risk factors include uremia, hyperhomocysteinemia, malnutrition, impairment of calcium and phosphorus metabolism, increased oxidative stress and chronic micro inflammation. Chronic micro inflammation and uremia are found to play a significant role in the pathogenesis of endothelial damage in CKD patients.

There are evidences to show that a decline in renal function is associated with endothelial dysfunction and inflammation (2). These are the two important and related early factors for the genesis of atherosclerosis (3). The novel biochemical markers of endothelial dysfunction and inflammatory activity have been found to be independent risk factors of cardiovascular complications in CKD patients (4-6). Many epidemiologic studies have shown that hs-CRP could independently predict the vascular risk and gives prognostic information also (7,8). Increased low density cholesterol (LDLc) and decreased high density cholesterol (HDLc) levels are associated with a high risk of cardiovascular complications in CKD patients (9). There are few studies which could show the effect of biomarkers of inflammation such as hs-CRP and lipid levels in CKD patients. Hence we have proposed in our study to estimate the levels of novel inflammatory markers hs-CRP and lipid parameters which increases the cardiovascular risk several times in CKD patients.

MATERIALS AND METHODS

Study design and subjects

This cross-sectional study was conducted in 50 CKD patients selected from the Department of Nephrology, Sri Ramachandra Medical College and Research Institute (SRMC and RI), Chennai. Ethical committee clearance was obtained from the Institutional Ethical Committee before the patients were inducted into the study.

The inclusion criteria were CKD patients of both genders aged between 20 to 65 years, who were on medical management and haemodialysis. The exclusion criteria were individuals who were treated for coronary artery disease, Cushing syndrome, obesity, cancer, autoimmune disorders or on drugs like oral contraceptive pills, anticancer drugs, anti-inflammatory drugs, phosphate binders, calcium supplements and steroids.

Data collection and parameter measurements

Patients background information with medical history, and anthropometric measurements were recorded; background information included age, sex, alcohol consumption, smoking status, nonsteroidal anti-inflammatory drug use, hypertension, diabetes mellitus, and hyperlipidemia. Metabolic parameters like hs-CRP, total cholesterol, HDLc, LDLc, triglycerides, calcium, phosphorus, urea and creatinine were estimated. The level of hs-CRP was measured by immunoturbidimetry method and other parameters measured by standard methodologies in the Hospital Central Laboratory, Sri Ramachandra Medical College & Research Institute, Porur, Chennai.

Statistical analysis

Statistical analysis was done using R Statistics Version 4.02. A *P* value < 0.05 was considered statistically significant. Obtained data was subjected to Kolmogorov–Smirnov test to check for the normal distribution of various variables. Based on the levels of serum hs-CRP the study participants were divided into three groups as low, medium and high. The variables were compared by one-way analysis of variance (ANOVA). Pearson correlation test was used to find the association between the variables.

RESULTS

A total of 50 CKD patients were included with a median age of 56 (49- 63) years (Table 1); among them, 23 patients were diabetic and 27 non-diabetic.

The individuals were classified into three groups as shown in Table 2. Depending upon hs-CRP levels, they are divided as Low (<0.80 mg/L), Medium (0.81–1.76 mg/L) and High (>1.76 mg/L). Serum creatinine level showed significant increase (*P*=0.007) across the three groups. Other variables did not show statistical difference (Table 2). Hs-CRP had a significant positive correlation with creatinine and negative correlation with HDLc (Table 3).

Table 1: General characteristics of the study population

Variables	Median [range]
Age (yr)	56.30 [49.20-63.50]
DM/NDM (n)	23/27
Fasting Glucose (mg/dL)	105.0 [83-163.8]
BUN(mg/dL)	47 [36.25-61.0]
Creatinine (mg/dL)	6.05 [4.35-9.07]
Calcium (mg/dL)	8.90 [8.15-9.30]
Phosphorus(mg/dL)	5.10 [4.12-6.27]
hsCRP (mg/L)	18.00 [3.26-67.0]
Total Cholesterol (mg/dL)	152.5 [121.1-185.2]
Triglycerides (mg/dL)	101.00 [78.25-180.0]
HDL(mg/dL)	35.50 [26.0-44.75]
LDL(mg/dL)	94.0 [76.75-121.0]
Total Cholesterol: HDL ratio	4.10 [3.30-5.07]

Table 2: Distribution of the variables and hs-CRP levels among the hs-CRP groups

Variables	hs-CRP levels (mg/L)			*P* value
	Low (<0.80 mg/L)	Medium (0.81–1.76 mg/L)	High (>1.77 mg/L)	
Age (yr)	37.0±12.72	47.0 ±11.40	58.02±11.57	**0.01**
Fasting glucose	75±2.82	109.75±17.89	134.91±15.90	0.059
BUN	40±8.48	72.00±29.43	51.18±21.34	0.14
Creatinine	6.28±2.67	8.80±3.20	11.30±4.70	**0.007**
Calcium	9.20±0.14	8.60±0.66	8.88±1.25	0.83
Phosphorus	5.70±0.9	6.40±1.67	5.37±2.06	0.62
Cholesterol	124.±12.72	138.70±51.35	162.25±68.76	0.6
Triglycerides	62.50±9.19	117.0±30.36	161.88±46.08	0.58
HDL	38.50±9.67	37.09±14.72	34.50±2.12	0.94
LDL	78.50±12.02	91.0±39.88	102.59±47.29	0.7
Total cholesterol: HDL ratio	3.60±0.56	3.50±0.69	4.57±1.66	0.34

DISCUSSION

Present study showed that hs- CRP levels increased in CKD patients and this is concurrent with the previous studies with hs- CRP levels increased up to five times in CKD patients as compared to controls. In this study, hs-CRP is a novel inflammatory biomarker of endothelial dysfunction and is involved in initiation and progress of atherosclerosis in CKD patients was positively correlated with creatinine and negatively correlated with HDLc (10). Hs-CRP is one of the biomarkers of choice to assess the cardiovascular risk due to its accuracy, accessibility, availability of standards for proper calibration and superior assay precision when compared to other acute-phase reactants.

Table 3: Association between hs-CRP and other parameters of the study population

Variables	Correlation Coefficient (r)	P-value
Fasting Glucose	0.1	0.48
BUN	0.22	0.11
Creatinine	0.27	**0.04**
Serum Calcium	0.2	0.15
Serum Phosphorus	0.004	0.97
Serum Cholesterol	-0.17	0.21
Triglycerides	0.23	0.09
HDL	-0.36	**0.008**
LDL	-0.16	0.26
Total Cholesterol: HDL ratio	0.25	0.07

The measurement methodology of hs-CRP is specific and is well standardized in contrast to the measurement methodologies of other inflammatory markers. According to the US Centre for Disease Control and Prevention (CDC) and the American Heart Association (AHA) guidelines, low risk for cardiovascular disease is defined as hs-CRP <1 mg/L, average risk as 1 to 3 mg/L, and high risk as >3 mg/L (11). Hs-CRP is considered to be a sensitive indicator of inflammation of endothelium, and further tissue damage. The concentration of this is associated with future development of atherothrombotic events. By its capacity to bind to lipoproteins and also by activating classic complement pathway, contributes to atherogenesis. Also it interferes with nitric oxide pathway (12). In concordance with our findings, many epidemiological studies revealed that hs-CRP is an independent factor of vascular events (13). Pearson *et al*., have reported that hs-CRP indicates increased cardiovascular risk in CKD patients (11)

Patients in the high hs-CRP group had high fasting glucose, high total cholesterol and high total cholesterol: HDL ratio. The present study showed that serum creatinine levels differed across the groups of CKD patients. This is concordant with Stuveling *et al*., study and they have concluded that higher levels of CRP concentration were strongly related with lower eGFR in non-diabetic population (14). Other studies also reported that in older populations, high CRP concentration was associated with higher serum creatinine levels, lower eGFR with higher CKD risk (15).

We have estimated the level of lipid parameters in CKD patients which showed that moderately elevated levels of triglycerides, LDL cholesterol and decreased levels of total cholesterol and HDL cholesterol (Table 2). Studies have shown that in CKD patients, the levels of HDL cholesterol which function as anti-inflammatory, antioxidant and also having role in the prevention of endothelial damage,

is decreased in CKD patients (16,17). The present study did not show any correlation between hs-CRP and other variables such as glucose, minerals, LDLc, total cholesterol and triglyceride (Table 3). Research evidences showed that persistently elevated CRP levels have biologic effects on vascular endothelium, coagulation, fibrinolysis, LDL oxidation and stability of atherosclerotic plaque (18). Hs-CRP helps to assess cardiovascular risk, monitor the progression of disease as per ACC/AHA Guidelines; thus reducing atherosclerotic cardiovascular risk in CKD patients (19).

CONCLUSION

Hs-CRP, a novel inflammatory biomarker was significantly elevated and this could diagnose endothelial dysfunction across the stages of renal impairment. Hs-CRP can be considered a surrogate marker which could be implemented as a screening test to assess the levels of inflammation and to implement intervention strategies to reduce hs-CRP levels and low density lipoprotein cholesterol levels. This is possible by lifestyle modifications and drugs to prevent cardiovascular complications earlier in the disease of CKD patients.

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CONFLICT OF INTEREST

All the authors in this study declare that there were no conflicts of interest during the study and also during the publication process.

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