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## Original Research Article

## Acute phase reactants in hemodialysis patients in relation to ejection fraction

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## ABSTRACT

Chronic Kidney Disease (CKD) is considered a public health problem because of its high prevalence, morbidity and mortality.<sup>1</sup> Morbidity remains high with more than 20% of patients undergoing hemodialysis dying every year with frequent complications of heart disease, hypertension, anaemia, inflammation and physical function.<sup>2</sup> Coronary artery disease has accounted for 40-50% of deaths among patients who undergo dialysis. Myocardial infarction has approximately accounted for 10-20% of these deaths which occur shortly after initiating dialysis with 29% within 1 year and 52% within 2 years. The risk increases as the kidney function declines.

The present study aims to study the serum levels of hs-CRP and ferritin in hemodialysis patients and to correlate with ejection fraction as an indirect association of coronary artery disease and therefore to study the role of inflammatory markers hs-CRP and ferritin in hemodialysis patients and their role as predictive markers in coronary artery disease.

The study included 50 hemodialysis patients with CAD and 50 hemodialysis patients without CAD. hs-CRP and ferritin parameters were analysed. hs-CRP and ferritin levels were significantly increased in hemodialysis patients with CAD ( $p < 0.000$ ) and the ejection fraction in patients on hemodialysis with coronary artery disease was significantly low ( $p < 0.000$ ). From the above values we can infer that hemodialysis patients with CAD have less ejection fraction when compared to hemodialysis patients without CAD. In conclusion, there was a significant elevation in the hs-CRP and ferritin levels when compared to controls furthermore it was also associated with worse prognosis for cardiovascular diseases.

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## 1. Introduction

Patients with chronic kidney disease progressing to end stage renal disease (ESRD) are at increased risk of coronary artery disease (CAD). In patients undergoing hemodialysis, the incidence of myocardial infarction (MI) has accounted for 10-20% of the deaths within the first year of dialysis progressing to 52% within 2 years suggesting an increased risk as the kidney function declines.<sup>3</sup> High sensitive C-reactive protein (hs-CRP) an acute phase reactant has been associated with increased incidence of atherosclerosis and cardiovascular mortality in hemodialysis patients.

Though being a non-specific marker of inflammation it has been as an independent predictor of cardiovascular events. Serum ferritin though reflects iron store is an acute phase reactant. It is increased due to the stimulatory effect of inflammatory cytokines which in turn leads to macrophage accumulation and increased in reactive oxygen species.<sup>4</sup> Timely identification and treatment of hemodialysis patients with LV dysfunction is important since it is the major factor predisposing to sudden death. Early interventions can help improve and eliminate the complications and slow the progression of kidney failure. Therapy at early stages and measures to improve can help eliminate most of the complications and slow the progression of kidney failure and improve the quality of

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life.<sup>5</sup> In this study the correlation between hs-CRP and ferritin and LV dysfunction as indicated by ejection fraction has been studied in hemodialysis patients.

## 2. Materials and Methods

A cross-sectional study was carried out at Owaisi Hospital and Research Centre (OHRC), Hyderabad. The study was conducted for a period of 1.5 years from 1<sup>st</sup> March 2017 to 1<sup>st</sup> September 2018 and was performed in the Department of Biochemistry in Deccan College of Medical Sciences (OHRC) in association with Dept. of Nephrology, OHRC. A total number of 100 patients were selected for the present study based on the inclusion and exclusion criteria. Patients were divided into two groups. Group 1 included no of patients on hemodialysis with CAD and Group 2 included no of patients on hemodialysis without CAD. All the patients more than 18 years who were on Dialysis attending Dept. of Nephrology, OHRC Hyderabad were included. Patients younger than 18 years, patients with acute infections, patients who have undergone CABG and patients who have undergone PTCA before initiation of dialysis were excluded from the study. Data for the study was collected from all those who fulfil the inclusion criteria after taking a detailed case history and obtaining a written informed consent. This study was approved by the Medical Ethics Committee of this institution.

## 3. Method of collection of data

Demographic and clinical data were recorded at the time of study entry, including age, gender, BMI, primary renal disease, co-morbidities and medications. CAD was diagnosed based on the history of angioplasty, CABG, myocardial infarction or angina, findings of regional wall valvular abnormality or reduced ejection fraction. Echocardiography was performed on a non-dialysis day.

### 3.1. Biochemical analysis

Blood samples were collected after an informed written consent. Under strict aseptic conditions, 5ml of venous blood sample was collected by venepuncture in plain vacutainers (red); sample was allowed to clot and centrifuged before processing. For the hs-CRP and ferritin, particle enhanced immunoturbidimetry method was used on Cobas C311 fully automated chemistry analyser. All the analytes estimated were subjected to standard quality control (QC) guidelines. The clinical biochemistry laboratory of Owaisi Hospital and Research Centre is a participant of External Quality Assurance Scheme (EQAS) from CMC Vellore. Internal Quality Assessment was run twice daily (12 hourly) with both first party controls (Cobas-PCC1, PCC2) and third party controls (Randox).

### 3.2. Statistical analysis

All the data so collected was duly recorded and complied; results and observations drawn and subjected to descriptive statistical analysis using MS Excel 2016 and Window stat version 9.3 from indostat services software. Values were expressed as mean  $\pm$  standard deviation (SD). \*p-value  $< 0.05$  which is statistically significant. \*\*p-value  $< 0.01$  which is statistically highly significant.

## 4. Results

The present study aims to analyse the serum levels of hs-CRP and ferritin in hemodialysis patients and to correlate with ejection fraction as an indirect association of coronary artery disease and therefore to study the role of inflammatory markers hs-CRP and ferritin in hemodialysis patients and their role as predictive markers in coronary artery disease.

Table 1 shows comparison of levels (Mean  $\pm$  SD) of hs-CRP, Ferritin and Ejection Fraction of cases and controls studied.

The study included 50 hemodialysis patients with CAD and 50 hemodialysis patients without CAD.

The (mean  $\pm$  SD) of ejection fraction (%) without CAD is  $54.67 \pm 7.40$  and (mean  $\pm$  SD) of ejection fraction with CAD is  $42.80 \pm 8.92$ .

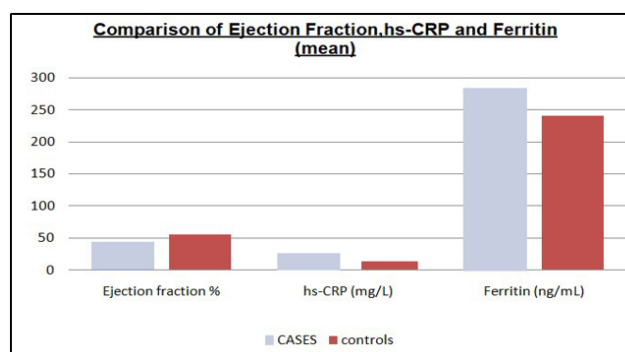
The (mean  $\pm$  SD) of hs-CRP (mg/L) with CAD is  $2.25 \pm 0.037$  and (mean  $\pm$  SD) of ejection fraction without CAD is  $0.88 \pm 0.08$ .

The (mean  $\pm$  SD) of ferritin (ng/mL) with CAD is  $281.82 \pm 30.677$  and (mean  $\pm$  SD) of ejection fraction without CAD is  $240.00 \pm 37.60$ .

The t and p value obtained for ejection fraction is 7.291 and 0.000.

The t and p value obtained for hs-CRP is 108.592 and 0.000.

The t and p value obtained for ferritin is 6.093 and 0.000.



**Fig. 1:** Comparison of means of Ejection fraction, hs-CRP and ferritin

The graph obtained shows that hemodialysis patients with CAD (cases) have high hs-CRP, high ferritin and low

**Table 1:** Comparison of levels (Mean± SD) of hs-CRP, ferritin and ejection fraction

Variable	Controls-Without Cad		Cases-with Cad		t-value	p-Value
Total no of subjects	50		50			
	Mean	S.D	Mean	S.D		
Ejection Fraction %	54.76	7.405	42.80	8.92	7.291	0.000 ***
hs-CRP(mg/L)	0.886	0.081	2.251	0.037	108.592	0.000 ***
Ferritin(ng/mL)	240.00	37.608	281.82	30.677	6.093	0.000 ***

\* is statistically significant (p-value < 0.05).

\*\* / \*\*\* is statistically highly significant (p-value < 0.01)

ejection fraction when compared to hemodialysis patients without CAD (controls). Graph shows that hemodialysis patients with CAD have less ejection fraction with a mean of 42.8 when compared to hemodialysis patients without CAD with a mean of 54.76, hemodialysis patients with CAD have high hs-CRP levels with a mean of 2.251 when compared to hemodialysis patients without CAD with a mean of 0.886 and hemodialysis patients with CAD have high ferritin levels with a mean of 281.82 when compared to hemodialysis patients without CAD with a mean of 240.00.

#### 4.1. Correlation of the levels of acute phase reactants with ejection fraction

By applying Pearson's product moment co-relation we found that the R value of hs-CRP vs EF (%) is -0.064 which is negatively related and R value of ferritin vs EF% is -0.1049 also negatively related.

## 5. Discussion

End Stage Renal Disease patients on hemodialysis have high morbidity and mortality and increased risk of cardiovascular complications.<sup>6</sup> Our results showed a significant increase (p < 0.000) in levels of ferritin and hs-CRP in hemodialysis patients with coronary artery disease as compared to hemodialysis patients without CAD. The ejection fraction was also significantly low (p < 0.000) in patients with coronary artery disease on hemodialysis. These findings were in accordance with a study by Liuzzo et.al who reported increased concentration of hs-CRP in patients who had recurrent angina, MI and were associated with increased readmissions for myocardial infarction.<sup>7</sup> Several other studies also reported a strong correlation between hs-CRP and cardiovascular events in hemodialysis patients and have pointed out that hs-CRP can be a powerful independent predictive factor of cardiovascular mortality and morbidity in hemodialysis patients. Further it was found that the risk of coronary artery disease in hemodialysis patient's increase as the duration of hemodialysis increased.<sup>7-9</sup> Several multicentric studies have reported a positive relation between mortality and morbidity in hemodialysis patients with ferritin. Excess iron leads to accelerated production of free radicals and increased lipid peroxidation.<sup>10</sup> Ferritin is an acute phase protein whose synthesis is regulated by

iron when there is absolute iron deficiency. However, once iron is available as regularly supplemented in hemodialysis patients the level of ferritin is regulated by other factors like inflammation.<sup>11</sup> Our study showed increased levels of hs-CRP and ferritin both of which being considered acute phase reactants and markers of inflammation. These markers are associated with high risk of atherosclerosis. Some studies have demonstrated the presence of CRP in atherosclerotic plaques in acute coronary syndrome, suggesting that atherosclerosis is characterized by low-grade inflammation besides lipid accumulation.<sup>12</sup> Increased translation of mRNA, ferritin subunits via IL-1 $\beta$  and TNF- $\alpha$  is seen during inflammation associated with reduction in iron mobilization. An increased in serum ferritin results from leakage of tissue ferritin. CKD is a major independent risk factor for cardiovascular morbidity and mortality with studies showing co-relation between the decrease in eGFR and increased risk of cardiovascular morbidity.<sup>13</sup> Presence and severity of left ventricular hypertrophy and dilatation and decreased ejection fraction are also independent predictors of cardiovascular death in ESRD patients. Due to the risk of cardiac ischemia and congestive heart failure, LV dysfunction in CKD patients is of complex nature and influenced by increased preload and left ventricular hypertrophy microvascular abnormality.<sup>14</sup> Further in our study, ejection fraction showed negative co-relation with acute phase reactants. Hence it is suggested that monitoring of acute phase reactants and cardiac status (EF) will help to take necessary steps to prevent or delay any cardiac event in hemodialysis patients.

## 6. Conclusion

Based on the findings of our study and other studies, hs-CRP and ferritin can be used as a novel inflammatory biomarker to predict cardiovascular events in patients with hemodialysis along with monitoring of ejection fraction.

## 7. Source of Funding

None.

## 8. Conflict of Interest

The authors declare that there is no conflict of interest.

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