Original Research Article

Correlation of Inflammation and Anemia in Patients on Hemodialysis

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Abstract

Introduction: Anemia and inflammation are majorly observed complications in patients on hemodialysis (HD). Present study assessed that inflammation that affects the haemoglobin levels in patients with chronic kidney disease (CKD) stage 5 on maintenance HD and to evaluate the degree of anemia.**Methods:** A retrospective observational study was conducted in CKD patients aged 18-89 years. Previous hospital records were reviewed to note baseline clinical co-morbidities, pre- and post HD -session body weight, dialyzer type, blood flow rate, dialysis time, dialysis prescription (dry body weight, dialysis time, dialysis modality, and dialysate and heparin dose). **Results:** Out of 46 patients on HD, 31 and 15 were dialyzed with the arteriovenous fistula (AVF) and tunneled cuffed catheters (CTC), respectively. The mean age was 54.59 years and majority had diabetic nephropathy (39.1%). Patients of AVF group showed decreased c-reactive protein (CRP) levels [10.49 (13.25) Vs 26.69 (20.0) mg/L] and higher dialysis vintage (35.50 vs. 15.07 days) as compared to CTC group. A significant negative correlation of CRP with hemoglobin ($p<0.0001$) and serum albumin ($p=0.0005$) was observed. CRP levels showed a positive correlation with erythropoietin resistance index (ERI) ($p=0.0025$). The mean serum CRP levels in patients having hypoalbuminemia (28.87 mg/L) were significantly elevated as compared with patients with normoalbuminemia (10.61 mg/L) ($p<0.001$). The mean ERI in patients with parathyroid hormone (PTH) value >300 pg/mL was comparatively higher (17.85) as compared to patients with PTH value <300 pg/mL (12.46).**Conclusion:** Reduced inflammation improves anemia and nutritional status of patients on HD. AVF should be considered as first option for dialysis access.

Keywords: Anemia, Inflammation, Chronic Kidney Disease, Hemodialysis.

Introduction

Majority of patients with end stage renal disease (ESRD) report anemia as a common complication, which progresses with the deterioration of renal function. Data from the Indian chronic kidney disease (CKD) Registry indicates increasing trend in the incidence & prevalence of anemia with the advancement of CKD stage 1 to stage 5[1]. Additionally, inflammation is also observed in most of the patients on hemodialysis (HD) and is multifactorial in origin[2].

In patients on HD, there is a need to create a dialysis access before initiating a treatment and it can be done using an arteriovenous fistula (AVF), cuffed tunneled catheters (CTC) or grafts. The CTCs are associated with an increased inflammation even when not associated with infection. This inflammatory milieu is associated with worse metabolic and clinical outcomes. Inflammation also induces hyporesponsiveness to erythropoiesis-stimulating agents (ESA) in patients on HD[3,4].

The present study assessed the factors including inflammation that affect the hemoglobin levels in patients with CKD stage 5 on maintenance HD and to evaluate the degree of anemia.

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Methods

Study Design

This was a retrospective observational study conducted in the Artificial Kidney Department, Topiwala National Medical College & B.Y.L Nair Charitable Hospital, Mumbai. The study was conducted over a period of 10 months. Patients with CKD stage 5 receiving HD in our institute or other dialysis centers in Mumbai who were having follow-up with us were selected for this study.

Ethics

The study protocol was approved by Institutional Ethics Committee and was conducted in accordance with the ethical standards provided in Declaration of Helsinki and its later amendments. Written informed consent was obtained from all patients before enrolment in the study.

Inclusion and Exclusion Criteria

Study inclusion criteria were patients aged 18-89 years, who were undergoing HD treatment thrice-weekly for at least 6 months, had a body weight of <100 kg, were in stable clinical condition, had not switched to peritoneal dialysis or other modalities and received ESA at least once a month for six consecutive months. Patients with clinically relevant infections, iron deficiency, haemoglobinopathies, sickle cell anemia, thalassemia or malignancies, active systemic diseases, active hepatitis or cirrhosis, unstable diabetes, diuresis >200 mL/24 h, a dysfunctioning vascular access with a blood flow rate of <300 mL/min or on corticosteroid therapy were excluded from the study. Patients who had experienced vascular access thrombosis, stroke, myocardial infarction, heavy blood loss, or who had

undergone major surgery or blood transfusion in the previous 3 months were also excluded.

Study Procedure: Previous hospital records were reviewed to note baseline clinical co-morbidities(hypertension, diabetes,ischemic cardiomyopathy, peripheral arteriopathy and a previous transient ischemic attack), pre- and post-session body weight, blood pressure and heart rate, dialysis parameters including filter type, blood flow and dialysis time. Data related to the dialysis prescription (dry body weight, dialysis time, dialysis modality, and dialysate and heparin dose) were evaluated and recorded monthly. Patients' weight, height and BMI were also recorded. Dialysis vintage was defined as the duration of time between the first day of dialysis treatment and the first day that the patient entered the cohort.

HD Treatment: HD was performed with low-flux polysulfone and a bicarbonate-based dialysate with systemic anticoagulation with heparin. Dialysate flow rate of 500 mL/min was used. The quality and quantity of saline infusions, ESA treatments, iron and any other drug administered orally or intravenously during or at the end of the session and all interdialysis therapies were recorded for each session. ESAs were administered subcutaneously and iron supplements were administered through the venous blood line at the end of the dialysis sessions. In catheterized patients, all dressings were changed at each dialysis treatment to inspect for signs of exit site infection. All exit sites were cleaned with a standard betadine solution after each treatment before re-dressing. All catheters had heparin instilled to prevent thrombosis between HD treatments. All study patients used dialyzers as per their body surface area and reused them 3-5 times. Adequacy of dialysis was ensured.

Statistical Analysis: Data were analyzed using SPSS version 26. Categorical variables were presented as number and percentages while, continuous variables were presented as mean and standard deviation (SD). Correlation analysis was performed using Pearson correlation coefficient. P-value <0.05 was considered as statistically significant.

Results

Out of total 73 patients studied, 46 patients on HD were enrolled and 27 were excluded because of the underlying infection or other exclusion criteria mentioned. Out of these, 31 patients were dialyzed with the AVF for 6 months or more, while 15 patients did not have fistula maturation and were dialyzed with CTC.The mean age was 54.59 years (range: 18-89 years) with 30 (65.2%) men and 16 (34.8%) women. The average BMI was 21.77 kg/m^2. Majority of patients had diabetic nephropathy (39.1%) followed by chronic glomerulonephritis and systemic inflammatory disease (including systemic lupus erythematous and vasculitis) (8.6% each). Other renal diagnoses were renal vascular disease (including nephrosclerosis; 6.5%), interstitial nephritis (including pyelonephritis; 4.3%), and polycystic kidney disease (2.1%) (Table 1).

The mean hemoglobin and serum albumin levels were similar (10.93 mg/dL and 10.35 mg/dl, and 3.78 g/dL and 3.51 g/dL, respectively) in the patients dialyzed with AVF and CTC. Patients of AVF group showed decreased c-reactive protein (CRP) levels [10.49 (13.25) Vs 26.69 (20.0) mg/L] as compared with patients of CTC groups. The mean erythropoietin (EPO) dosage and erythropoietin resistance index (ERI) were slightly reduced in AVF group (138.79 IU/kg/week and 13.48, respectively) as compared with CTC group (154.57 IU/kg/week and 15.39, respectively). The mean dose of ESA was 8258.06 IU/week in AVF group and 10000 IU/week in CTC group. The average dialysis vintage was higher in AVF group (35.50 days) as compared with CTC group (15.07 days) (Table 2).In complete study population, a significant negative correlation of CRP levels with hemoglobin levels (r=-0.59, p<0.0001) and serum albumin levels (r=-0.50, p=0.0005) was observed. CRP levels showed a significant positive correlation with ERI (r=0.44, p=0.0025) (Figure 1A-C). A significant negative correlation of ERI was observed with hemoglobin levels (r=-0.50, p=0.0004) as well as serum albumin levels (r=-0.43, p=0.003). In patients dialyzed with AVF, CRP levels were negatively associated with hemoglobin (r=-0.59, p=0.0005) and serum albumin levels (r=-0.52, p=0.003); while serum albumin levels were positively associated with hemoglobin levels (r=0.656, p<0.0001). Similarly, in patients dialyzed with CTC, CRP levels showed negative correlation with hemoglobin (r=-0.626, p=0.013) and positive correlation with ERI (r=0.58, p=0.024). Serum albumin levels were positively correlated with hemoglobin levels (r=0.614, p=0.015) and serum creatinine levels (r=0.625, p=0.013); while negatively correlated with ERI (r=-0.55, p=0.035).The mean (SD) serum CRP levels in patients having hypoalbuminemia (defined as <3.5 g/dL) (28.87 [16.37] mg/L) were significantly elevated as compared with patients with normal albumin levels (10.61 [14.99] mg/L) (p<0.001). The mean ERI in patients with parathyroid hormone (PTH) value >300 pg/mL was comparatively higher (17.85 [8.00]) as compared to patients with PTH value <300 pg/mL (12.46 [7.99]) (Figure 2). No significant difference was observed in ERI between the patients with TSAT >30% (13.315 [7.80]) and those with TSAT in the range of 20-30% (15.579 [9.23]).In a multiple linear regression analysis, only access type was significantly associated with higher CRP concentrations (with a β-coefficient of -2.256) independent of age, gender, diabetes status. Serum albumin levels (β-coefficient= -0.243; p=0.005) and age (β-coefficient= -6.516; p=0.0007) were the best predictors of EPO resistance in HD patients. When albumin was excluded from the analysis, the best predictors of EPO resistance were age (β-coefficient= -0.252; p=0.001) and transferrin levels (β-coefficient= -0.051; p=0.049). When both albumin and CRP were excluded from analysis, low transferrin levels predicted high EPO resistance.

Table 1: Baseline characteristics

Baseline characteristics	Total (n= 46)
Age, mean (SD)	54.59 (16.42)
Range	18-89
Sex	
Men	30 (65.21)
Women	16 (34.78)
BMI (Kg/m^2), mean (SD)	21.77 (4.1)
Renal diagnoses	
Diabetic nephropathy	18 (39.13)
Chronic glomerulonephritis	4 (8.69)
Systemic inflammatory disease	4 (8.69)
Renal vascular disease	3 (6.52)
Interstitial nephritis	2 (4.34)
Polycystic kidney disease	1 (2.17)
Miscellaneous and unknown diagnoses	14 (30.43)

Data shown as n (%), unless otherwise specified.
BMI, Body Mass Index.

Table 2: Distribution of clinical parameters across the study groups

Parameters	AVF (n=31)	CTC (n=15)	Total (n=46)
Hemoglobin (g/dL)	10.93 (1.82)	10.35 (1.86)	10.74 (1.84)
Serum albumin (g/dL)	3.78 (0.51)	3.51 (0.47)	3.69 (0.51)
CRP levels (mg/L)	10.49 (13.25)	26.69 (20.0)	15.78 (17.33)
EPO/Kg/week dosage	138.789 (61.99)	154.572 (90.55)	143.935 (71.90)
ERI (erythropoietin resistance index)	13.479 (7.39)	15.390 (10.10)	14.102 (8.29)
ESA dose (IU/week)	8258.0 (3809.79)	10000 (4519.80)	8826.09 (4088.22)
Dialysis vintage	35.50 (44.42)	15.07 (10.59)	-

Data shown as mean (SD).
AVF, arteriovenous fistula; CTC, tunneled cuff catheter; CRP, C-Reactive Protein; EPO, erythropoietin; ERI, erythropoietin resistance index; ESA, erythropoiesis-stimulating agent.

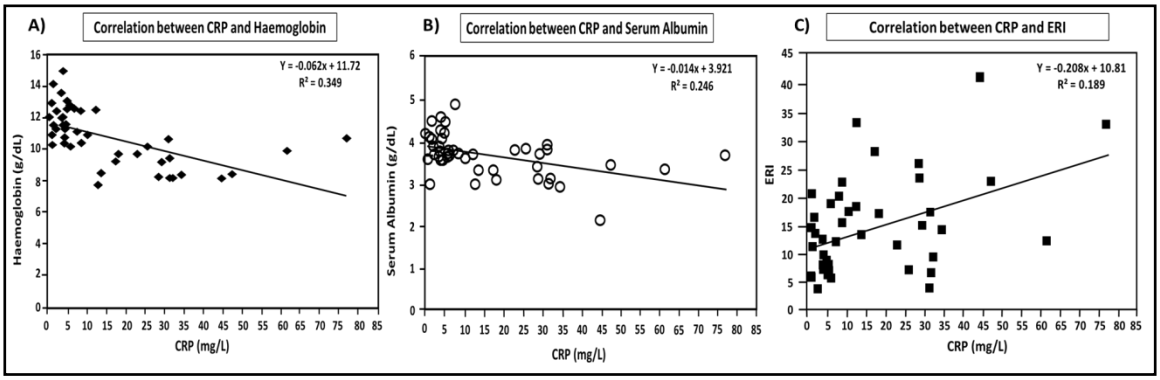

Figure 1: Association of CRP levels with hemoglobin, serum albumin and ERI across the study population.
Correlation between (A) CRP and hemoglobin (B) CRP and serum hemoglobin and (C) CRP and ERI.
CRP, C-Reactive Protein; ERI, erythropoietin resistance index.

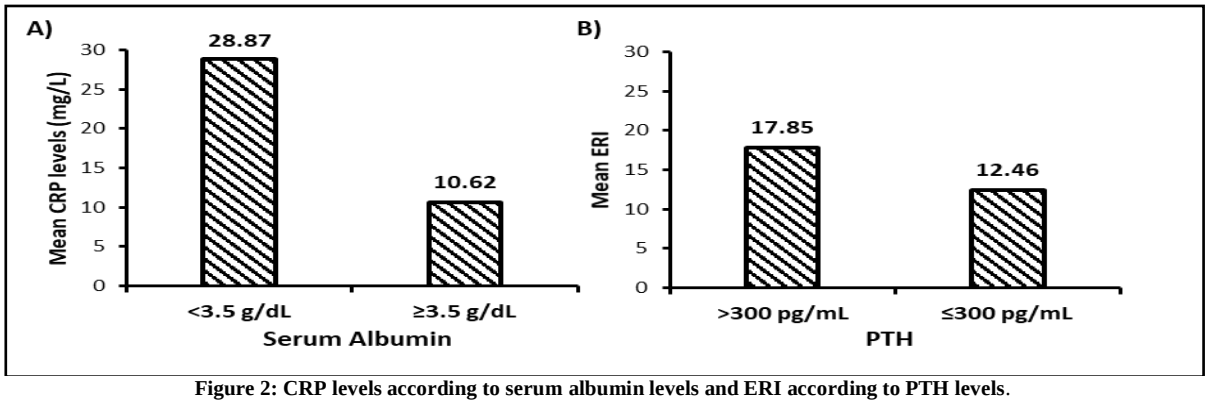

Figure 2: CRP levels according to serum albumin levels and ERI according to PTH levels.
CRP, C-Reactive Protein; ERI, erythropoietin resistance index; PTH, parathyroid hormone.

Discussion

The present study was conducted with the aim to demonstrate that vascular access affects hemoglobin levels and need for ESAs in patients on HD. Even though there was no demonstrable evidence of infection in dialysis patients, an elevated CRP levels were observed in the CTC group. The CTC group also had lower hemoglobin and albumin levels with a higher ERI despite being adjusted for other parameters. Inflammation was also observed in the patients dialyzed with AVF but it was less as compared to the CTC group. Inflammation also increases the need for ESA which are associated with its own set of complications. Increased ESAs also means increased expenditure which in a developing country like India will be a financial burden on the family and society as a whole.

In the present study, the mean age was 54.59 years with a mini mum of 18 years and a maximum of 89 years. Men were prevalent accounting for 65.2%. A 2011 report of CKD registry of India indicated similar observation with mean age of 50.1 years and 70.6% men. The reason for the progression of renal failure may be the delay in detecting the renal disease, late referral, and failure to introduce preventive measures. Rajapurkar M, et al. reported diabetic nephropathy (31.3%) as the commonest cause of CKD in all geographic areas followed by CKD of miscellaneous and undetermined etiology (27.7%) and chronic glomerulonephritis (13.8%)[4]. Present study results concord with these observations (diabetic nephropathy, 39.13%; miscellaneous and unknown diagnoses, 30.43%; and chronic glomerulonephritis, 8.69%).

This study evaluated whether an elevated CRP levels correlates to a decreased hemoglobin concentration in patients on HD. A previous study by Baranay P, et al. analyzed the relationship between CRP levels and the dose of human recombinant EPO required to maintain hemoglobin levels at approximately 12 g/dL. They reported that the EPO doses and CRP were both inversely correlated to the levels of serum albumin and serum iron, suggesting the link between the principle mechanism by which inflammatory cytokines inhibit erythropoiesis and functional iron deficiency[5]. The present study also demonstrated use of CRP as a predictor of resistance to EPO

treatment. When patients were subdivided according to CRP <20 mg/L or ≥20 mg/L, the mean ERI was 12.87 and 16.92, respectively. This observation has clinical relevance suggesting patients would require higher dose of ESA. However, there are multiple adverse effects of high dose ESA. Further, the present study demonstrated a significant negative correlation of CRP levels with hemoglobin levels ($p<0.0001$) indicating increased CRP levels correlate with decreased hemoglobin levels. Overall, these results demonstrate link between inflammation and anemia in these patients.

Erythropoietin (EPO) resistance was defined by the ratio of the weekly EPO dose to hemoglobin, yielding a continuously distributed variable (EPO/Hb). Serum albumin level (β-coefficient= -0.243; $p=0.005$) and age (β-coefficient= -6.516; $p=0.0007$) were the best predictors of EPO resistance in HD patients. When albumin was excluded from the analysis, the best predictors of EPO resistance were age (β-coefficient= -0.252; $p=0.001$) and transferrin levels (β-coefficient= -0.051; $p=0.049$). When both albumin and CRP were excluded from analysis, low transferrin levels predicted high EPO resistance. High EPO/Hb occurred in the context of high ferritin and low transferrin levels, the pattern expected in the acute- phase response, not in iron deficiency. These results are similar to those shown in a study by Gunnell J, et al[6].

This study also evaluated association of hemoglobin with serum albumin and serum creatinine levels in patients. Serum albumin levels showed positive association with hemoglobin levels ($r=0.653$, $p<0.0001$) indicating positive relationship between nutrition and anemia. This finding was also observed by others in a study done by Madore F, et al[7].Hypoalbuminemia is a marker for visceral protein depletion, which may contribute to impaired erythropoiesis and anemia. Visceral protein deficiency could adversely affect heme and erythrocyte synthesis, as well as iron transport, storage, and utilization. It could also affect erythropoietin production. It is noteworthy that the serum albumin concentration directly correlated with erythropoiesis, while serum creatinine concentration correlated inversely.

Serum CRP levels in hypoalbuminemia patients were significantly elevated compared with normoalbuminemic dialysis patients ($P<0.001$). Similar results were seen in a study done by Danielski M, et al[8]. A recently published study assessed the mortality risk with low serum albumin and its dependence on concomitant systemic inflammation in patients with CKD stage 5. They reported an increase in the mortality risk in these patients with decreased serum albumin and elevated CRP as compared with patients with low serum albumin and normal CRP. Overall observations suggested that inflammatory status should be considered when using serum albumin for risk assessment in patients with CKD stage 5[9].

This study determined if type of vascular access affects hemoglobin in these patient population. Access type was significantly associated with higher CRP concentrations independent of age, gender, and diabetes status. Comparative analysis of CRP levels between patients dialyzed with AVF and CTC showed significant difference. The elevated CRP levels might have led to an increase in ERI and decrease in serum albumin which was observed in these patients. A significant negative correlation between CRP and serum albumin in both study groups, while a positive correlation between ERI and CRP only in the CTC group was reported. Present study demonstrated patients from AVF group were associated with lower CRP and ESA requirements and higher hemoglobin values. This study also tried to characterize features of erythropoiesis whose correction might enhance ESA responsiveness and correct anemia. A PTH value of more than 300 corresponded to higher ERI as compared with a PTH value of less than 300. This indicates that a better control of secondary hyperparathyroidism will help reduce the ESA dose. A study by Kalantar-Zadeh K, et al. reported the case-mix adjusted odds ratio of the greatest vs. poorest ESA responsiveness at patient level for Intact PTH=600 pg/mL (reference: 150-300 p/ml) was 0.54 (95% CI: 0.49 to -0.60)[10]. Besarab A, et al. found that HD patients whose TSAT was in the 30-50% range for 6 months had a 40% reduction in administered ESA dose compared to patients whose TSAT remained in the 20-30% range[11].The present study did not observe significant difference in ERI between the patients with TSAT >30% and those with TSAT in the range of 20-30%. It is better to consider not giving excess IV iron in view of its oxidative potential.

Limitations

Retrospective analysis, small sample size and short duration of follow up are our major limitations.

Conclusion

These observations confirmed that if inflammation could be reduced in these patients, an improvement in their anemia and nutritional status could be possible. This study only adds to the plethora of evidence that use AVF as the first option dialysis access in patients undergoing HD. Further studies using various anti-oxidants are required to see if they can help reduce the inflammation and improve anemia in this population.

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