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Original Research Article

Anemia and inflammation, a link between end stage kidney disease and left ventricular hypertrophy

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ABSTRACT

Background: Based on Glomerular Filtration Rate (GFR) Chronic Kidney Disease patients are classified into five stages. It starts with early stage of CKD and finally ends with End Stage Kidney Disease (ESKD). Anemia and inflammation are major medical complication in End Stage Kidney Disease and leads cardio vascular complications like LVH.
Methods: A cross sectional study carried out over a 2 year period in Department Nephrology and General Medicine OPD, MIMS, Vizianagaram, Andhra Pradesh, India 120 in which 60 are normal healthy individuals and 60 are End stage kidney Disease. In all the participants Serum creatinine, blood urea, Serum Iron, TIBC, TSAT% Serum ferritin, Serum CRP, IL-6 and TNF-α was measured. All the EDTA blood samples were analyzed for complete blood count.
Results: The diagnostic criteria for CKD like blood urea and serum creatinine were significantly higher in ESKD. There is a significantly increased level of Left ventricular mass index in ESKD when compared with Control. The mean erythrocyte indices are decreased in ESKD. The mean serum iron, TIBC and TSAT% decreased ESKD. Whereas serum ferritin significant increase in ESKD group and the mean serum CRP IL-6 and TNF-α significant increase in ESKD group when compared with control
Conclusion: Present study finding suggested that there is a raised inflammatory marker in ESKD patients due to inflammation and it further changes serum ferritin, serum iron and TIBC. The above altered factors leads to changes in erythrocyte indices and leads to anemia which ends with cardiovascular complication like Left Ventricular Hypertrophy.

Keywords: Anemia, End stage kidney disease, Inflammation, Left ventricular hypertrophy

INTRODUCTION

Chronic Kidney Disease (CKD) there is loss of nephrons and irreversible sclerosis. The renal mass gradually declined over a prolonged period. Based on Glomerular Filtration Rate (GFR) Chronic Kidney Disease patients are classified into five stages.[1] It starts with early stage of CKD and finally ends with End Stage Kidney Disease (ESKD). In End Stage Kidney Disease the treatment is renal transplantation or hemodialysis. The major etiology for increased incidence of CKD are Diabetes and hypertension.[2] Anemia is the one of the major medical complication in CKD. Anemia is noticed from early stages of CKD and further exacerbated in End Stage Kidney Disease.[3]

Anemia also causes adverse complications like cardiovascular death and it can be overcome by repeated

blood transfusion and Erythropoietin (EPO) therapy with iron. Erythropoietin (EPO) therapy with iron will cause free radical formation and associated complications. Repeated blood transfusion leads to infections and iron overload.[4]

In End Stage Kidney Disease anemia is due to decreased erythropoietin synthesis and iron deficiency. The kidney function declines the EPO deficiency associated with increased anemia and in ESKD anemia is still further aggravated.[5] In ESKD patients the RBC half-life is reduced due to decreased EPO bone marrow fail to respond. Uremia toxins also causes anemia by suppression of bone marrow and activation of apoptosis.[6]

Iron deficiency is most common in ESKD patients and the causes are declined intestinal absorption, surgical blood loss due to Ateriovenous (A.V) fistula, loss of blood via dialysis process.[7] The deficiency still further high in End stage kidney disease patients without iron theraphy. Acute and chronic inflammatory state in ESKD is further causative factor for anemia.[8] Increased proinflammatory cytokines in inflammatory state also causes the decreased production of erythropoietin and apoptosis of CFU-E.[9]

CKD patients even in the moderate impairment will also shows low grade inflammation and it is still further raised in ESKD by raising the polymorphonuclear leuckocytes and CD14/CD16.[10] It is also noticed that inflammatory molecules like CRP, IL-6 and TNF-α contribute for suppression bone marrow erythropoiesis, suppression of erythropoietin production and intestinal bleeding.[11] And also causes raised hepcidin in which will prevent iron absorption from intestine and contribute iron deficiency.[9]

All the above factors contribute for anemia and it further leads to cardiovascular complications especially left ventricular hypertrophy (LVH). LVH is a physiological adaptation due to increased myocardial work over a long period. It occur due to pressure or volume overload. In anemia heart compensate for decreased pepherial oxygen delivery and leads to hypertrophy. As hypertrophy progresses capillary density decreases and further causes death of myocytes.[12] Both anemia and LVH are highly prevalent in ESKD.

METHODS

The study was a Case-Control study. Study population are patients and attendants who attend the Department of Nephrology and General medicine. It takes 2 year period that is from July 2017 to July 2019. 120 in which 60 are normal healthy individuals and 60 are ESKD patients.

Inclusion criteria

The patients attending General medicine and Nephrology Department diagnosed with ESKD.

Exclusion criteria

Known Subjects with history of smoking, alcoholism and medicines. Patients with any debilitating illness also excluded. ESKD patients who did not provide inform constant were excluded

Study design

The study consists of 60 ESKD patients and 60 normal healthy individuals, age and sex matched individuals. Informed consent will be taken from the patients and controls. Demographic data will be collected followed by history regarding current health status, history of medication, alcoholism and Active smoking. A questionnaire was given to all patients and detailed clinical examination was performed.

In all the participants blood pressure measured by using mercury sphygmomanometer both systolic and diastolic blood pressure was measured based on 1st and 5th korotkoff phase. An average of two readings was considered

All the participants are subjected 12 lead Electrocardiography and recorded at paper speed 25mm/s and 1-mV/cm calibration. LVH defined based on Sokolow-lyon voltage criteria the amplitude of the S wave in lead V1 and the R wave in lead V5 or V6 is more than 3.5 mV was considered as LVH.[13] LVH was further confirmed by using 2D echocardiography the data was recorded based on American Society of echocardiography guidelines. LVH was confirmed based on Framingham criteria were LV mass index greater than 131 g/m2 in male and more than 100g/m2 in female. Interventricular septum wall thickness or the posterior wall if >1.2 cm was considered as LVH.[13]

Sample analysis

The blood samples were collected into a test tube containing anticoagulant and then mixed gently on the blood mixer. RBCs count, Hb concentration, hematocrit Hct%, haematimetric indices (MCV, MCH, and MCHC), RDW, WBCs and platelets counts were measured using automated blood cell counter (Sysmex KX-21 analyzers). The serum samples were used for Blood urea estimation by GLDH - Urease method.[14] Serum creatinine was estimated by Jaffes method.[15] Based on serum Creatinine eGFR was estimated by using MDRD formula.[16] The serum iron and TIBC was estimated by Ferrozine method.[17] based on the serum iron and TIBC transferring saturation (TSAT%) was calculated. The ferritin, CPR, IL-6 and TNF-α was estimated by using standard ELISA kit of AccuBind Laboratories.

Statistical analysis

Data will be expressed in Mean and Standard deviation (mean±SD). Z test was used for comparison of means

between controls and cases. The statistical significance was determined at 5% ($p< 0.05$) level.

RESULTS

The present study was conducted at Maharajah's Institute of medical sciences, vizianagaram, Andhra Pradesh, India. A total of 120 subjects were included. They are 60 ESKD patients and 60 Normal healthy individual as control.

Table 1: Profile of control and ESKD.

	Control	ESKD
Number	60	60
Age (mean±SD) years	47.31±10.29	48.15±12.91
Sex (Males %)	61	63
(Females %)	49	47
Blood urea (mg/dl)	21.54±6.27	88.35±18.92**
Serum Creatinine (mg/dl)	0.78±0.15	8.95±2.54**
eGFR (mL/min)	98.89±7.54	18.27±8.67**
Blood pressure (mm Hg) Systolic	110.14±9.17	158.86±25.28**
Diastolic	74.28±7.93	94.21±8.24**
Left ventricular mass index (g/m^2)	107.54±9.68	129.72±17.25**

**P<0.001

Table 1 shows the mean age of the ESKD was 48.15 years±12.91 Control it was 47.31years±10.29. As regards the sex distribution, the majority of subjects were male in ESKD 63% and Control 61%. The diagnostic criteria for ESKD like blood urea, serum creatinine were significantly higher in ESKD when compared to Control and the mean eGFR in ESKD (18.27ml/min±8.67) is having lower value as compared to the mean value of Controls (98.89ml/min±7.54). This decrease is statistically significant ($p <0.001$). In the present study systolic and diastolic blood pressure was significantly increased in ESKD compared with Control. It is also reported that mean Left ventricular mass index in ESKD (129.72 g/m^2±17.25) is having higher value as compared to the mean value of Controls (107.54 g/m^2±9.68). This increase is statistically significant ($p <0.001$).

Table 2 shows Erythrocyte Indices in this the mean serum RBC count in ESKD (3.72±0.38) is having lower value as compared to the mean value of Controls (4.25±0.32). This decrease is statistically significant ($p< 0.001$). It is also reported that mean Hb in ESKD (9.2±0.65) is having lower value as compared to the mean value of Controls (12.92±0.38). This decrease is statistically significant ($p<0.001$).It is also reported that the mean Hct, MCV, MCH and MCHC are also decreased in ESKD patients when compared to control. The decrease is statistically significant ($p<0.001$).

Table 2: Comparative study of erythrocyte indices in control and ESKD.

Parameter	Control	ESKD
RBC X 10^6/µl	4.25±0.32	3.72±0.38**
Hb (g/dl)	12.92±0.38	9.2±0.65**
Hct (%)	38.54±1.18	30.85±2.24**
MCV (fl)	89.87±4.53	80.98±5.95**
MCH (Pg)	32.12±1.98	24.99±3.42**
MCHC (g/dl)	33.78±1.21	31.32±2.24**

**P<0.001

Table 3 shows that mean serum Iron in ESKD (62.92 µg/dl±12.24) is having lower value as compared to the mean value of Controls (91.25 µg/dl±11.98). This decrease is statistically significant ($p <0.001$). The mean serum TIBC and TSAT% in ESKD is having lower value as compared to the mean value of Controls. This decrease is statistically significant ($p<0.001$). It is also reported that mean serum ferritin in ESKD (878.52 ng/ml±270.42) is having higher level as compared to the mean value of Controls (120.24 ng/ml±14.54). This increase is statistically significant ($p <0.001$).

Table 3: Comparative study of serum iron profile in control and ESKD.

Parameter	Control	ESKD
Serum Iron (µg/dl)	91.25±11.98	62.92±12.24**
Serum TIBC (µg/dl)	282.12±9.45	219.55±38.65**
Serum TSAT (%)	31.65±4.35	30.21±7.54**
Serum ferritin (ng/ml)	120.24±14.54	878.52±270.42**

**P<0.001

Table 4: Comparative study of serum CRP and IL-6 in control and ESKD.

Parameter	Control	ESKD
CRP (mg/L)	1.24±0.18	3.28±0.24**
IL-6 (pg/ml)	1.11±0.09	2.21±0.78**
TNF-α (pg/ml)	1.45±0.11	2.84±0.45**

**P<0.001

Table 4 shows that mean serum CRP in ESKD (3.28 mg/L±0.24) is having higher value as compared to the mean value of Controls (1.24 mg/L±0.18). This increase is statistically significant ($p<0.001$). The mean serum IL-6 in ESKD (2.21 pg/ml±0.78) is having higher value as compared to the mean value of Controls (1.11 mg/L±0.09). This increase is statistically highly significant ($p <0.001$). It is also reported that mean serum TNF-α in ESKD (2.84 pgml±0.45) is having higher value as compared to the mean value of Controls (1.45 pg/ml±0.11). This increase is statistically significant ($p<0.001$).

DISCUSSION

In End Stage Kidney Disease patients there is an increased blood urea and serum creatinine level due to decreased glomerular filtration. In ESKD patients there is uncontrolled blood pressure due to hypervolemic state. In ESKD anemia and inflammation are cofounders and causes poor oxygen delivery and raised stroke volume and leads to left ventricular hypertrophy.

In ESKD patients all the erythrocyte indices are decreased compared with control. The hormone erythropoietin causes erythropoesis and there is a deficit of erythropoietin in ESKD patients. In ESKD patients at the site erythropoesis there is a diminished iron availability it is due to gastrointestinal bleeding, loss of blood from dialysis process, decreased intestinal iron absorption and frequent blood draw for investigation. All these factors contribute to decreased level of erythrocyte indices.[18]

In ESKD patients there is decreased serum iron value this may be due to raised inflammation state, more GI blood loss, erythropoietin therapy, which direct serum iron to the site of erythropoesis and blood loss during dialysis. During inflammation hepcidine is synthesized in large amount from liver. It causes internalization and degradation of ferroportin, which is responsible for iron efflux from the cell. There is failure in absorption of intestinal iron and also inhibition of iron release from reticuloendothelium system (RES) to transferrin and causes iron retention by RES.[19]

Due to the inflammation transferrin decreased in ESKD patients. Transferrin is negative acute phase protein in inflammation transferrin level will be decreased that leads to decreased TIBC value. Transferrin binds with iron and transport iron to target site. Transferrin is synthesized in liver and it level is increased in iron deficiency and raised level of estrogen and progesterone.[20] Decreased level of transferrin are present in infections, liver disease and malignancy. While calculating Transferrin saturation percentage (TSAT%) serum iron in the numerator and TIBC present as denominator and TSAT% altered due to parallel decrease of both serum iron and TIBC. In ESKD patients due to inflammation there is a decreased level of transferrin this will leads decreased TIBC level.[21]

In ESKD patients adequate iron will be maintained by administering intravenous iron it may raises the hemoglobin value. The intravenous iron inhibit phagocytosis and promote survival of microorganism and susceptible to infection.[22] In ESKD patients there is malnutrition, raised intracellular calcium and increased plasma factors all contribute to inhibition of neutrophil function all the factors to exacerbated infection. Hemodialysis process itself precipitates the inflammatory state and repeated access to blood vessels for hemodialysis can also causes recurrent infections.[23]

In inflammation process the inflammatory cytokines like TNF-α, andIL-6 are raised it will further cause increased translation of ferritin mRNA and leads to raised serum ferritin.[24] This high ferritin level trap the iron and prevent the adverse effect of infection because free iron is responsible for formation of free radical and causes cell damage and inflammatory process. The raised ferritin causes functional iron deficiency and it is helpful in acute inflammation but in chronic inflammation it causes anemia. This phenomenon was supported by earlier study of increased IL-6 in ESKD patients.[25]

From the findings of present study, it was concluded that there is a raised value of CRP, IL-6 and TNF-α in ESKD patients. Due to inflammation it causes increased ferritin and decreased TIBC and lowered serum iron and this further cases changes in erythrocyte indices and leads anemia. Anemia causes poor oxygen delivery and increased stroke volume and leads left ventricular hypertrophy. Early detection and correction of these abnormalities will reduce progression adverse effects.

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