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Original Research Article

Clinico-pathological correlation study in chronic kidney disease patients undergoing hemodialysis

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ABSTRACT

Background: Chronic Kidney Disease (CKD) is a global health problem and associated with increased morbidity and mortality. Hemodialysis is the most common mode of renal replacement in end stage kidney disease. Variation in hematological and biochemical parameters are the prime factors responsible for morbidity and mortality in CKD patients. Normocytic Normochromic Anemia is a typical morphology seen in CKD patients resulting due to erythropoietin deficiency. Early detection and treatment of these pathologies can improve the quality of life in CKD patients.

Objectives: 1) To evaluate the clinical manifestations and various pathological changes associated with CKD patients on hemodialysis. 2) To compare and correlate various clinico-pathological parameters in CKD patients on hemodialysis, with special emphasis on diabetic kidney disease.

Materials and Methods: One year eleven months retrospective study was done at CIMS hospital, which included 50 CKD patients. Complete clinical data were recorded and correlated with various hematological and biochemical parameters. Statistical analysis was performed by chi square test and student's T test.

Results: Out of 50 CKD patients, 86% were male, age group of 41-50 years (62%). The commonest co-morbidity was combined hypertension with diabetes in 44%. Majority (72%) had BP between 140-159mmHg. Most (64%) of the CKD patients were known cases of diabetes. Significantly lower levels of RBC count, hemoglobin, hematocrit and platelet count were found with normocytic normochromic anemia being the commonest morphological type. Significantly increased WBC counts, ESR, serum urea, creatinine and serum phosphate levels were noted in CKD patients. DKD patients showed significant risk compared to NDKD patients.

Conclusion: CKD is a progressive, irreversible disease. We found alterations in various haematological and biochemical parameters, which were more severe among DKD patients compared to NDKD patients. Early recognition and management of these changes will have an important impact in improving the quality of life.

1. Introduction

Chronic kidney disease (CKD) also known as chronic renal failure (CRF) is a clinical disorder resulting from change in structure or function of kidney and is characterised by slow, progressive and irreversible damage in renal function. CKD patients usually remain asymptomatic for a longer time and presents with complications associated with renal dysfunction only at advanced stage.[1] It is a highly prevalent condition in general adult population with great burden and requires very high cost of care especially, in developing countries like India.[2]

Based on recent study, Nephrology's Kidney Disease Data Centre Study reported a prevalence of 17% internationally.[3] In India, diabetes and hypertension today

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account for 40–60% cases of CKD.[4] High blood sugar in diabetic patients damages small blood vessels throughout the body including kidney. Patients with diabetes can develop high blood pressure as well as rapid hardening of the arteries, which can also lead to heart disease and eye disorders.[5]

Since 19th century, the management and treatment of chronic kidney disease has changed drastically because of newer studies and research technologies.[2] Hemodialysis is one of the most commonly employed renal replacement therapy in CKD patients when kidney transplantation is not possible. There are two main types of dialysis, known as hemodialysis and peritoneal dialysis.[6]

Pathological changes associated with derangement in haematological and biochemical parameters are the prime factors responsible for morbidity and mortality in CKD patients.

Normocytic Normochromic Anemia (NNA) is a typical morphological anemia seen in CKD patients resulting due to erythropoietin deficiency, blood loss and shortened red cell life span.[7]

Absolute IDA was defined as transferrin saturation (TSAT) <20% and/or ferritin <100 ng/mL. Functional IDA was defined as TSAT < 20% and ferritin 100–500 ng/mL.[8] Functional iron deficiency is mainly due to increased levels of hepcidin.

Chronic inflammation plays an important role in the progression of chronic kidney disease which is proved by high levels of inflammatory mediators associated with reduced renal function.[9] Platelet dysfunction is also common in patient with renal insufficiency.[10] Early detection and management of these pathologies can improve the quality of life in CKD patients.

The main objective of the present study is to evaluate the clinical manifestations and various pathological changes associated with CKD patients on hemodialysis and to compare and correlate various clinico-pathological parameters in CKD patients on hemodialysis, with special emphasis on diabetic kidney disease.

2. Materials and Methods

A cross-sectional study was carried out in the Department of Pathology, of CIMS teaching hospital over a period of one year two months from January 2019 to December 2020. The study was initiated after taking approval from Institution Ethics Committee.

Known cases of Chronic Kidney Disease patients who where on maintenance hemodialysis were included in the study population. Newly diagnosed kidney disease and patients who were on renal replacement therapy other than hemodialysis were excluded from the study.

A pre-tested structured questionnaire was prepared to collect the clinical data and pathological investigations. Clinical data regarding the gender, age, underlying comorbid conditions for developing CKD, presenting complaints, individual's blood pressure and random blood sugar were recorded at the beginning of study. Haematological and biochemical parameters like RBC count, hemoglobin, hematocrit/PCV, RDW, Red cell indices, WBC count, Platelet count, peripheral blood smear, ESR, iron studies, renal function tests and serum potassium were tested. Blood samples were collected in EDTA anticoagulant tube for haematological investigations like RBC count, hemoglobin, PCV, WBC count, ESR etc. Blood samples were collected in plane tube without anticoagulant for biochemical investigations. Haematological and biochemical parameters in CKD patients were compared with normal control values and correlated with special emphasis on diabetic CKD patients.

Statistical package for social sciences (SPSS-Version 21) was used to carry out the statistical analysis of data. Results are expressed as Mean +/- and Standard deviation in the form of tables. Chi-square test is used for comparison of categorical variables. Student T-test was used for comparison of quantitative data between two groups. The analysis was done in the form of percentages and proportions and represented as tables.

3. Results

Out of 55 proven cases of CKD patients undergoing hemodialysis who were included in the study, 50 patients were followed up throughout the study and 5 patients were lost to follow up. In our study among 50 CKD patients undergoing hemodialysis majority, 43 patients (86%) were male and only 7 patients (14%) were females. Patient's age ranged from 31 to 75 years. Maximum number of CKD patients presented in the age group of 41 to 50 years (62%) followed by 51-60 years (18%) and 31 to 40 years, 61 to 75 years comprising for 10% each (Table 1).

Table 1: Age and gender distribution of CKD patients

Age distribution	Males	Females	Total cases
31-40	4	1	5 (10%)
41-50	27	3	31 (62%)
51-60	7	2	9 (18%)
61-75	4	1	5 (10%)
	43 (86%)	7 (14%)	50 (100%)

In our study, we found common co-morbid conditions leading to CKD were hypertension combined with diabetes in 22 patients accounting for (44%), followed by diabetes in 12 patients (24%), hypertension in 10 patients (20%), coronary artery disease in 3 patients and chronic obstructive pulmonary disease in 3 patients comprising for (6%) each (Table 2).

The most common clinical presentation in CKD patients undergoing hemodialysis was pedal oedema 14 (28%), followed by headache 13 (26%), nausea and vomiting 7

Table 2: Distribution of CKD patients with underlying co-morbidities

Co-morbidities	No. of cases (%)
Hypertension + Diabetes	22 (44%)
Diabetes	12 (24%)
Hypertension	10 (20%)
Coronary artery disease	3 (6%)
COPD	3 (6%)

(14%), fever 5 (10%), pruritus 5 (10%), chest pain and breathlessness in 3 cases (6%) each (Table 3).

Table 3: Distribution of CKD patients with their clinical manifestations

Clinical manifestation	No. of cases (%)
Pedal Oedema	14 (28%)
Headache	13 (26%)
Nausea & Vomiting	7 (14%)
Fever	5 (10%)
Pruritis	5 (10%)
Chest pain	3 (6%)
Breathlessness	3 (6%)

Blood pressure, systolic BP was recorded in all the 50 CKD patients at the beginning of study using sphygmomanometer in the brachial artery by auscultatory method. Elevated blood pressure was noted in 36 patients (72%), and rest of them ie., 14 patients (18%) had BP of <120mmHg. 22/36 patients (61%) recorded BP between 140-159 mmHg followed by 8/36 patients (22%) recorded BP of >160mmHg and 6/36 patients (17%) had BP between 120-139 mmHg (Table 4).

Table 4: Distribution of CKD patients based on blood pressure

BP range in mm Hg	No. of cases (%)
<120	14 (28%)
120- 139	6/36 (17%)
140-159	22/36 (61%)
>160	8/36 (22%)

Among 50 CKD patients, 32 patients we're known cases of diabetes. Random blood sugar was found to be 140-180 mg/dl in 4 patients (8%), 180-200 mg/dl in 10 patients (20%), and >200mg/dl in 18 patients (36%) (Table 5). Random blood sugar tested in remaining 18 (36%) patients who had no previous history of diabetes was found to be within normal limits ie.<140mg/dl.

Effect of Chronic Kidney Disease on haematological and biochemical parameters tested in our study has been presented in (Table 6)., shows that the RBC count, hemoglobin, hematocrit/PCV and platelet count were significantly lower in CKD patients (p-value <0.001) compared with mean control value in normal adults.

Table 5: Distribution of CKD patients based on random blood sugar

Random blood sugar in mg/dl	Diabetic CKD	Non-diabetic CKD
<140	-	18 (36%)
140-180	4 (8%)	-
180-200	10 (20%)	-
>200	18 (36%)	-
Total cases	32 (64%)	18 (36%)

Among 50 CKD patients, 45 (90%) of them were diagnosed to be anaemic, with hemoglobin level <12.5 gm/dl in females and hemoglobin <13gm/dl in males or PCV <35% in females and <40% in males, majority of them (62%) categorised under moderate anemia i e. Hemoglobin values between 7-10gm/dl and remaining (28%) were categorised under mild anemia ie. Haemoglobin values between (10-12.5gm/dl). Normocytic Normochromic Anemia was the most common morphology seen with peripheral smear in (75%), RDW and other red cell indices were within normal range in these patients. In remaining (25%) patients Microcytic Hypochromic Anemia was the morphological anemia seen on peripheral blood smear with increased RDW and MCV MCH and MCHC were in lower limits of normal range.

Iron studies done revealed reduced serum ferritin in 32/50 (64%) of CKD patients. However, serum iron, transferrin saturation and total iron binding capacity was found to be within normal limits in 28/50 (56%) of CKD patient in our study. By definition, in the present study iron deficiency anemia was found to be more prevalent than functional iron deficiency among CKD patients.

Renal function tests revealed significant elevated levels of serum creatinine and blood urea in CKD patients compared with normal controls (p-value <0.001). Serum potassium was found to be mildly elevated in majority of CKD patients 31/50 (62%) and was found to be within normal range in remaining 19/50 patients (38%).

Haematological and biochemical parameters were compared and correlated between diabetic CKD patients (DKD) and non-diabetic CKD patients (NDKD), presented in (Table 7). In our study we found significant reduction in RBC count, hemoglobin and hematocrit/PCV in DKD patients when compared with NDKD patients. However, platelet count tested in DKD and NDKD patients did not show any significant difference. Majority of DKD patients were categorised under moderate anemia ie. Hemoglobin values between 7-10gm/dl and peripheral smear showed Normocytic normochromic anemia in these patients, with normal red cell indices.

The possible evidence for association between inflammation and diabetes can be found in our study, total White Blood Cell counts and ESR was found to be significantly higher in DKD patients when compared

Table 6: Descriptive statistics of various haematological and biochemical parameters in CKD patients

Parameters	CKD patients Mean	SD	Controls Mean	SD	t Test	P. value
RBC count (million/cumm)	3.76	0.58	4.5	0.79	5.33	<0.0001
Hemoglobin (gm/dl)	9.96	1.35	14.25	1.22	16.67	<0.0001
PCV/Hematocrit (%)	25.87	5.15	39.5	3.02	16.14	<0.0001
Platelet count (lakhs/cumm)	1902.19	13434.71	28600.00	10500.00	11.07	<0.0001
MCV (femtoliter)	88.34	6.01	89.57	6.07	0.88	0.38
MCH (picograms)	28.92	1.50	29.5	1.78	1.56	0.123
MCHC (gm/dl)	33.54	1.57	34.00	2.22	1.37	0.1734
RDW (%)	13.56	1.32	13.28	1.11	0.94	0.334
WBC count (per microliter)	13410.89	4178.15	7300.76	2097.00	7.45	<0.0001
ESR (mm/hr)	27.36	8.92	14.00	8.51	6.60	<0.0001
Total serum iron (mcg/dL)	101.26	19.80	105.00	28.13	0.694	0.489
Serum Ferritin (mcg/L)	23.89	64.65	157.4	80.73	8.075	<0.0001
Transferrin saturation (%)	28.61	10.61	31.44	9.37	1.205	0.231
TIBC (mcg/dL)	266.85	71.83	289.20	68.24	1.372	0.174
Serum Creatinine (mg/dL)	7.92	2.50	0.65	0.14	15.89	<0.0001
Blood Urea(mg/dL)	121.21	47.24	26.7	7.2	10.85	<0.0001
Serum Potassium (mmol/L)	5.46	1.36	4.53	0.643	3.99	0.001

Table 7: Comparison of haematological and biochemical parameters between diabetic CKD patients (DKD) and non-diabetic CKD patients (NDKD)

Parameters	DKD patients Mean	SD	NDKD patients Mean	SD	t Test	P. value
RBC count (million/cumm)	2.23	0.43	3.98	0.83	9.85	<0.0001
Hemoglobin (gm/dl)	7.23	1.53	11.52	1.34	10.00	<0.0001
PCV/Hematocrit (%)	22.34	6.12	31.54	4.08	5.69	<0.0001
Platelet count (lakhs/cumm)	1803.46	12654.62	1901.23	11567.53	0.0027	0.978
MCV (femtoliter)	82.34	6.35	81.57	5.98	0.420	0.677
MCH (picograms)	26.35	3.29	28.12	2.78	1.93	0.06
MCHC (gm/dl)	32.12	4.63	33.54	3.82	1.10	0.274
RDW (%)	16.12	3.86	14.89	4.11	1.056	0.295
WBC count (per microliter)	16367.74	5078.15	11803.26	3045.21	3.501	0.001
ESR (mm/hr)	33.59	10.26	26.49	7.63	2.594	0.012
Total serum iron (mcg/dL)	99.43	20.83	100.63	26.98	0.149	0.881
Serum Ferritin (mcg/L)	23.64	65.85	27.83	58.93	0.218	0.829
Transferrin saturation (%)	22.69	14.76	27.47	15.21	1.154	0.254
TIBC (mcg/dL)	259.31	94.64	279.2	88.63	0.781	0.438
Serum Creatinine (mg/dL)	8.12	3.67	7.84	2.84	0.935	0.354
Blood Urea(mg/dL)	124.52	29.84	118.96	27.26	0.708	0.482
Serum Potassium (mmol/L)	6.16	1.67	5.98	1.23	0.234	0.816

with NDKD. Majority of DKD patients showed absolute increase in chronic inflammatory cells like lymphocytes and monocytes.

Iron studies, renal function tests and serum potassium done revealed no significant difference between DKD and NDKD patients in our study.

4. Discussion

In the present study, the mean age of CKD patients was 51 years which is higher compared to studies done by Low J et al.[11] and Rasheed N et al.[12] which showed mean age of 41 years and 31.3 years respectively. However, study done by Habib A et al.,[13] Ferdinand IM et al.[14] and Haythem Ahmed et al.[15] had similar findings with present study showing mean age of 50 years, 52.5 years and 51 years respectively. Thus, we conclude a significant association between increasing age and chronic kidney disease.

Male CKD patients were found to be significantly higher than female patients of same age group in our study with the male to female ratio of 6.1:1, similar findings were reported by Ferdinand et al.[14]

It has been observed in the present study that most common comorbidity underlying CKD was combined hypertension with diabetes (44%) in majority of the patients followed by diabetes mellitus in (24%) of CKD patients. Similar findings has been reported in study done by Habib A et al.[13] hypertension combined with diabetes accounting for 40% of the cases. We conclude that majority of the

CKD patients would have previous comorbid conditions like diabetes and or hypertension underlying. Thus, frequent monitoring of blood glucose and blood pressure in patients above 45years can help to reduce the risk of kidney disease.

Present study revealed statically significant association between low RBC count and reduced hematocrit in CKD patients ($p<0.001$) when compared with normal adult population. These findings correlated with study done by Alghythan A K et al.[16] and Al-Ageel N et al.[17] Degree of anemia progresses with severity of renal disease in CKD patients.[18]

In our study significantly reduced hemoglobin levels ($p<0.001$) and platelet count were observed in CKD patients compared with normal adult population, which was consistent with results of Habib A et al.[13] Suresh M et al.[19] and Turedi S et al.[20] Various factors like impaired erythropoietin synthesis, shortened lifespan of RBCs and suppressed bone marrow eythropoiesis are involved in reduced RBC counts and hematocrit in CKD patients which eventually decreases hemoglobin concentration.[21,22] Impaired erythropoietin secretion which alters the effect of megakaryocyte colony stimulating factors is the main cause for thrombocytopenia in CKD patients.[23,24]

Red cell indices in our study did not show any significant differences between CKD patients and healthy individuals, similar results were found in study by Alghythan A K et al.[16] and Ferdinand et al,[14] suggesting that normocytic normochromic anemia is the most common morphological type of anemia we encounter in CKD patients. However study done by Docci et al.[25] and Lippi et al.[26] showed higher RDW with mean value of 12-20% and 25.2% respectively in CKD patients.In most of these patients higher RDW was associated with lower MCV, MCH and MCHC suggesting microcytic hypochromic anemia being the second most common morphological type of anemia we encounter in CKD patients.

Further, iron studies done revealed insignificant changes in total serum iron, transferrin saturation and total iron binding capacity in the present study. We found serum ferritin was significantly low ($p<0.001$) in CKD patients compared with healthy adults.

Diebold, M et al.[27] concluded significant reduction in serum iron and serum ferritin in chronic renal failure patients undergoing hemodialysis. Tekce H et al.[28] revealed low transferrin level in end stage renal disease patients in their study done at Turkey (2014). Thus, regular evaluation of iron stores has to be done in CKD patients for adequate management of iron deficiency anemia.

Functional IDA was found to be associated with an increased risk of mortality and cardiovascular hospitalization, but absolute IDA was associated only with a higher risk of hospitalization.

The present study revealed higher WBC counts, with absolute lymphocytosis and monocytosis which is in agreement with Reddan DN et al.[29] and Alghythan et al.[16]

This can be explained by possibility of systemic inflammation which may serve as a risk factor for CKD development.[29] Up regulation of inflammatory mediators like tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6) results in activation of acute phase reactants such as C- reactive protein[30] which may be one of the main causes for elevated ESR value as seen in the present study associated with uremic stage in CKD patients. Similar results were found in study done by Habib A et al.[13]

A significant association ($p<0.001$) was observed between elevated blood urea level in CKD patients when compared with healthy adults in the present study. This finding is consistent with results of Haythem A et al.[15] and Ali S et al.[31] study done in India (2013). Chronic renal disease results in irreversible loss of renal function which in turn results in retention of nitrogenous substances with elevation of blood urea nitrogen and non-protein nitrogen. Raised serum creatinine was significantly associated with CKD patients ($p<0.001$), which is in agreement with results of Graves JW et al.,[32] study in USA (2008). Reduced urinary excretion of creatinine along with increased formation of metabolites through catabolic processes plays a role in elevated serum creatinine in CKD patients.[33]

In our study, we found significant increase ($p<0.001$) in CKD patients compared with healthy adults. Loss of phosphorus homeostasis due to excretion failure in chronic kidney disease results in hyperphosphatemia,[34] which is a major contributor for cardiovascular morbidity in CKD patients.

In present study special emphasis was given for diabetic kidney disease patients (DKD) from which we conclude that degree of anemia was more severe compared to non-diabetic kidney disease patients (NDKD), probable explanation could be that poor glycemic control associated with complications in diabetic patients. Morphologically normocytic normochromic anemia is the commonest type of anemia in DKD patients which is in agreement with Taderegew M M et al. Significantly higher WBC counts and ESR were associated with DKD patients in our study with possible explanation of association between elevated blood sugar and increased inflammatory activity in DKD patients.

5. Conclusion

Chronic Kidney Disease is a highly prevalent condition seen in increasing age group associated with greater impact on morbidity and mortality in these patients.

CKD is associated with abnormalities in different haematological and biochemical parameters that requires early investigation and treatment. Also, Diabetic Kidney Disease patients (DKD) show greater degree of risk compared to Non-Diabetic Kidney Disease (NDKD) patients. Normocytic normochromic anemia was

the commonest morphology seen in both DKD and NDKD patients. Abnormal renal function tests and hyperphosphatemia is associated with great cardiovascular mortality in CKD patients.

6. Source of Funding

None.

7. Conflict of Interest

None.

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