Original Article

Anemia chronic kidneys Disease

Coagulation Activation Markers and Anemia in Patients Presenting with Chronic Kidneys Disease

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ABSTRACT

Objective: To study coagulation activation markers and anemia in chronic kidney Disease patients.
Study Design: Comparative / cross sectional study.
Place and Duration of Study: The study was conducted at the Pathology Department of Hayatabad Medical Complex Peshawar (HMC) from Feb 2017 to May 2018.
Materials and Methods: In this study total of 100 patients of chronic kidney disease (CKD) were included and 50 individuals were taken as a control group. All patients of CKD were evaluated for anemia and hemostatic marker, i-e D-dimer, PT and APTT.
Results: A total of 95 (95%) of the patients were anemic. Mean Hemoglobin (Hb) level was 9.625±1.253 g/dl. Significantly low as compared with the control group. In 75% of CKD patients, D-dimer levels were elevated. Mean D-dimer level was in the range of 500-1000ng/µl, significantly elevated as compared to control group. 3 out of 100 CKD patients showed prolonged PT and 4 out of CKD patients showed prolonged APTT. Mean PT and APTT were 11.52± 1.562 seconds and 28.562±1.562 respectively. 5 out 100 CKD patients showed thrombocytopenia. Mean platelets counts were 150.562±10.562×1/µl. Similarly 6 out of 100 CKD patients showed prolonged BT mean BT as 12.562±1.265 minutes.
Conclusion: The study concluded that chronic kidney disease patients are significantly associated with anemia and hemostatic abnormality. Therefor proper attention should be given to these patients, as anemia and coagulation abnormality may lead to severe complications and increase morbidity and mortality from the disease. These patients should be properly managed regarding anemia and hemostatic abnormality, to improve their life style. Further work up and assessment is necessary in this regard to prevent any thromboembolic phenomenon.
Key Words: Chronic kidney disease, Anemia, Coagulation profile, D-dimer.

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INTRODUCTION

The US National Kidney Foundation's kidney dialysis outcomes quality initiative guidelines defines chronic kidney disease as kidney damage or estimated glomerular filtration rate of <60ml/min/1.73m^2 for more than 3 months.[1]

Both hematological and hemostatic abnormalities occur in chronic kidney disease. The major cause of anemia in CKD is lack of erythropoietin synthesis in diseased kidneys which is usually of normochromic normocytic.[2] predispose the patients to bleeding.[3]

Hemolysis, Iron deficiency, Folate and B12 deficiency are also contributing factor to anemia in CKD. Renal anemia is one of the most complication of chronic kidney disease and majority of the patients present with anemia.[4] CKD patients presenting with anemia has high risk of cardiovascular disease.[5]

Chronic kidney disease patients are also associated with coagulation disorder leading to thrombotic complications and this is the most common cause of death.[6]

The coagulation disturbance includes platelets dysfunction, vascular endothelium abnormality, fibrinolytic system and Von Willebrand factor (VWF) abnormality. VWF is secreted by endothelial cells and megakaryocytes and increases level of VWF is a sign of endothelial injury and risk of thrombotic events.[7] Fibrinogen, FVII and FVIII are important coagulation factors in coagulation system activation and these markers have been shown to associated with increased thrombotic events.[8] Increased levels of pro coagulant complex, D dimer, fibrinogen VWF, and protein C

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increase level of thrombotic embolism and heart failure.[9] D dimer is plasmin mediated photolytic degradation of fibrin clot, and its elevated levels shows thromboembolic phenomena in a patient presenting clot.[10]

The aim of the study is to evaluate the anemia and hemostatic markers in chronic kidney disease patients. As prothrombin time (PT), activated partial thromboplastin time (APTT), Bleeding time (BT) and D dimer levels immediate and early management of anemia improved patient life style and reduce further morbidity and mortality regulating from anemia and thrombotic complication in these patients.

MATERIALS AND METHODS

The study was conducted in the pathology department of Hayatabad Medical Complex Peshawar and medical department of the same hospital from February 2017 to February May 2018.

A total of 100 patients of chronic kidney disease were in the study and 50 individuals were taken as a control healthy individuals Patients were both males and females patients Septicemia, DVT (deep venous thrombosis), Malignancy, pregnancy, chronic disorders like SLE and Rheumatoid arthritis were excluded from the study.

Blood samples of 5ml were collected from each patients of chronic disease in a tube containing sodium citrate. The citrated tube were centrifuged to separate plasma for determination of D-dimer, PT and APTT.

Similarly sample of 2ml were also collected in EDTA tube for determination of hemoglobin level to indicate anemia. Hb levels were determined by hematology Analyzer cell dyn Ruby USA for the patients of chronic kidney disease. D-dimer levels were also performed on sample of all chronic disease patients, D-dimer is a fragments cross-linked fibrin clot, which has degraded plasmin. Its level increases in any condition where clot formation and its subsequent fibrinolysis occurs. So its elevated level indicate a hypercoagulable state and thromboembolic events in anywhere in the body system.

Minalex D-dimer is a latex agglutination test and give us semi quantitative results its procedure include take 20µl of plasma and 20µl od D-dimer and observe for agglutination with 180 seconds agglutination indicates positive value more than 250ng/µl. Then for further quantitation serial dilution of sample is done in which we dilute 100µl plasma in 100µl of normal saline in a plane tube and then 100µl is taken and put in another tube containing 100µl of normal saline this make a serial dilution for 1:2, 1:4, and 1:8 respectively which further elaborate the result of D-dimer as 250-500ng/ml, 500-100ng/ml and 100-200ng/ml. The same procedure for undiluted i-e 20µl of D-dimer mixed with 20µl of sample. Raised level of D-dimer indicates thromboembolic events in the body and give immediate information to the clinicians to go further supportive investigation to localize thrombosis.

PT and APTT were performed CP 3000 coagulation analyzer. These investigations indicate the activity of both extrinsic and intrinsic pathway.

All data were subjected to statistical analysis by sums chi square and T test level of significance set at $p<0.0022$ bleeding time were also performed on patients of chronic kidney disease. According to standard procedure normal bleeding time was denoted 7-9 minutes**.**

RESULTS

In total males and females all these patients of CKD were subjected to Hb level and hemostatic parameters

Table No.1: Frequency of anemia and abnormal hemostatic markers in chronic kidney disease (CKD)

S. No.	Anemia and Hemostatic parameters in CKD	Percentage
1	Anemia	90%
2	D-dimer	75%
3	PT	3%
4	APTT	4%
5		5%
6	Bleeding time	6%

Table No 2. Mean value of anemia and hemostatic parameter in chronic kidney disease. (CKD)

S No	**Anemia and hemostatic parameters**		**Mean of control group**
1	Anemia	9.625±1.253g/dl	12.56±1.562g/dl
2	D-dimer	40% 500-1000ng 35% 100-7000ng	<250ng/ml
3	PT	16.52±1.562 seconds	10.23±1.235 seconds
4	APTT	43.562±1.562	36.652±1.256 seconds
5	Platelet	120.5654±10.562 ×10*3/µl	350.562±15.256×10*3/µl
6	BT	12.562±1.265 minutes	7.520±1.256 minutes

that is D-dimer, PT and APTT. In our study 90% of patients were anemic. Hb level was 9.625±1.253gm/dl significantly lower as compared to control group D-dimer levels were $p<0.0023$ also studied 75% of the patients of CKD showed elevated D-dimer levels, 15 out of 100 had D-dimer level at the range of 250-50mg/ml. 40 out of 100 patients had D-dimer level at the range 500-100ns/ml and 30 out of 100 patients had D-dimer levels at the range of 100-200ng/ml. D-dimer was significantly elevated as compared to control group $p<.00326$. Similarly PT and APTT were also performed

on all these patients 3 out of 100 showed prolong PT and 4 out of 100 showed prolong APTT. Mean PT and APTT were 15.5±1.562 second and 43.562± 1.562 respectively. Similarly 5 out of 100 patients showed thrombocytopenia mean platelet counts was 120.5654±10.562 $\times 10^3/\mu l$ significantly lower as compare to control group p<.00325. Bleeding time were also assessed in chronic kidney disease patients 6 out of 100 showed prolonged bleeding time. Mean bleeding time was 12.5±19.26 seconds. Which were significantly higher as compared to control group p value p<.00326.

DISCUSSION

Chronic kidney disease is a condition associated with permanent loss of glomerular rate, which in turn leads to the development of uremia. High blood urea creatinine levels and accumulation of waste products effect and every system of the body, Anemia and coagulopathy is one of these effects.[10]

In the present study 85 out of 100 chronic kidney disease patients had anemia. Mean Hb level was 9.5±0.52gm/dl significantly lower as compared to control group mean Hb in control group were 13.5±1.256gm/dl.[11]

A similar study has been conducted by Mimura et al that majority of patients with CKD and associated with anemia.[12] Study of Juillerat JL et al. also show similar observation to study that anemia is common complication in CKD patients.[13] Go, As et. al also reported in their study that anemia is common in CKD patients.[14] The exact mechanism foe anemia in multifactorial, numerous studies suggest anemia in CKD is mainly due to eruthropoietin deficiencies.[15, 16] Other factors that contribute to anemia is circulating uremic induce inhibitor of erythropoiesis shortened red cell survival, metabolic and mechanical factor IV deficiencies disorders iron hemostasis and hepcidine excess all contribute anemia in CKD.[17, 18]

The national kidney foundation kidney disease outcomes quality initiative (NKF-KDOQI) guidelines 2000 recommended Hb targets should be generally maintained in the range of 11-12gm/dl.[19] The 2007 KDOQI guide lines indicate target Hb levels should not exceed 13g/dl as high Hb level exceeding 13.5g/dl is associated with composite events like death and stroke.[20]

In the presenting study hemostatic markers that is D-dimer, platelets counts, Bleeding time, PT and APTT were also studied. In our study D-dimer levels were elevated in 75% of chronic kidney disease patients. A similar study has been conducted by Mohammed Sadiq et al. that chronic kidney disease is associated with elevated D-dimer levels, in another study Miozzari M et al. also reported that elevated D-dimer level reported in chronic kidney disease patients.[21, 22]

Similarly 6 out of 100 patients of CKD showed prolong bleeding time. Mean bleeding time was 12.56±1.265 minutes. Different authors conducted with prolong study that chronic kidney disease is associated with prolong Bleeding time shows similar correlation to our study. [23, 24]

5 out of 100 chronic kidney disease showed thrombocytopenia mean platelets count was 120.565±10.562×10^3/µl. while rest of the patients have normal platelets count as compared to control group. Similarly 4 out of 100 chronic kidney disease had prolong prothrombin time and 3 out of 100 patient had prolong APTT. Mean PT value of prolong PT and APTT were 16.5± 1.562 seconds 43.562±1.562 seconds respectively as compared to control groups. A lot of studies conducted and reported that chronic kidney disease is associated with thrombocytopenia and prolong PT and APTT similar correlations had been reported Mohapatara et al.[25] Herman and Guffer also reported in their study that chronic kidney disease is associated with thrombocytopenia and prolong PT.[26, 27] Patients with chronic disease associated with coagulation abnormality and thromboembolic phenomenon is common findings among patients with chronic kidney disease.[28] VWF levels increase in CKD patients and has pro coagulants effect and risk for thrombotic events.[29] Fibrinogen, FVII and FVIII , D-dimer level also increases and associated with prevalence of thromboembolic complication.[30]

CONCLUSION

The study concluded that chronic kidney disease is associated with severe anemia and coagulation abnormalities as evidenced by low HB level and elevated D-dimer levels. Abnormal hemostasis and anemia both increase the risk for hospitalization and thrombotic events, which in turn leads to increase mortality and morbidity. Therefor the physician should strictly watch patients of CKD to maintain Hb level of such patients to a level to improve their life style and also take measure to reduce thrombotic complications in such patients which will further reduce the mortality and morbidity resulting from CKD.

Author's Contribution:

Concept & Design of Study:	Shahtaj Khan
Drafting:	Naveed Khan
Data Analysis:	Subhanuddin Babar Rehman Khatak
Revisiting Critically:	Shahtaj Khan Naveed Kham
Final Approval of version:	Shahtaj Khan

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