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HEMATOLOGICAL EFFECTS AND CARDIAC DERANGEMENT IN END STAGE RENAL DISEASE - A RETROSPECTIVE ANALYSIS

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ABSTRACT

INTRODUCTION

Anemia is one of the major disorders needing great attention in public. Anemia free India is a national project with a motto nourish, prevent and protect. According to NFHS 2024 67% children and 59% of adolescent girls are anemic. The WHO reports prevalence of anemia in 40% of children aged 6-59 months and 30% in 15-49 years. While iron deficiency and folic acid deficiency have been the major factors in malnutrition contributing to anemia, defective absorption of the supplemented nutrients is the second major problem. The prevalence of chronic kidney disease is in the exponential trend and Rounik tadulkar et al have estimated 13.24% prevalence in India. This data is further worrying and poses major threat to the management of anemia in the masses. Anemia refers to reduction in red cell mass or reduced hemoglobin and decreased oxygen carrying capacity of blood to tissues. It has significant effects on respiratory and cardiovascular systems and generalised effects due to reduced tissue oxygenation. This study is a retrospective analysis of hematological aspects of kidney disease derived from data in end stage renal disease patients who presented for renal transplantation. Reduced production and impaired morphology, increased destruction are all the changes that could cause anemia in chronic kidney disease. Apart from tissue oxygenation, anemia in ESRD causes associated coagulation abnormalities and significant cardiac dysfunction. Study of red cell width distribution enables to notify increased anisocytosis that provokes hemolysis and anemia. Through erythropoietin from juxtaglomerular apparatus takes the brunt of causation. Several uremic toxins attack various levels and components of anemia.

Methods: The case records, laboratory and echocardiogram reports of the patients who attended the preanesthetic clinic were scrutinised and the selected aforesaid parameters were noted. The results were tabulated and analysed.

RESULTS

Hemoglobin, red cell width and platelets showed negative correlation with r value of -0.015 with creatinine levels. A lower hemoglobin and PCV was associated with poor ejection fraction (p=0.01) and raised RVSP (P=0.05) .The values of ejection fraction and PCV showed p= 0.011, red cell width vs RVSP depicted p= 0.076, packed cells with EF showed p = 0.011, LA diameter with ejection fraction showed p= 0.004. Hemoglobin and ejection fraction showed a significant p value = 0.007.

CONCLUSION

Anemia in chronic kidney disease progresses with severity of the renal dysfunction. Erythropoietin, the cytokine hormone which is the major attribute of anemia, the production of which is directly proportional to the glomerular mass. Oxygen delivery to peripheral tissues is determined by red cell

mass. The red cell mass is controlled by variations in production of erythropoietin by negative feedback loop. This response of erythropoiesis production requires iron, vitamin B12 and folic acid as cofactors. Inefficient erythropoiesis due to vitamin B12 and folic acid causes megaloblastic anemia and iron deficient erythropoiesis leads to microcytic anemia. The red cell width distribution increases leading to hemolysis, tissue hypoxia and associated with raised RVSP (P= 0.076). This study includes hematological indices which have been analysed for right and left heart parameters that conclude severity of cardiac dysfunction to be associated with severe anemia. Poor PCV and hemoglobin associated with LVEF (p=0.01). Red cell width distribution with RVSP P = 0.076, LA diameter negatively correlating with hemoglobin p-0.06 and PCV (r= 0.18) signify strong association of cardiac involvement with anemia of ESRD. Correction of anemia appears to halt the progress of cardiac involvement which has been determined as the major cause of morbidity and mortality in patients with end stage renal disease.

KEY WORDS
Anemia, End stage renal disease, cardiorenal syndrome, Erythropoietin, right ventricular systolic pressure, Ejection fraction, LA diameter.

INTRODUCTION

The global features of chronic kidney disease include proteinuria, occult and visible blood loss, impaired cellular response to hypoxia and anemia. Anemia becomes more prevalent and severe with a declining glomerular filtration rate. At least 90% of dialysis dependant patients develop anemia. Both absolute and functional iron deficiency. Abnormal platelet functions, impaired prothrombin consumption, impaired iron processing, hypocellular marrow are some of the factors attributing to anemia and coagulopathies. Reduced erythropoietin and hepcidin decrease the lifespan of red blood cells. The compensatory mechanism to anemia such as hyper dynamic state, cardiac failure and cardiomyopathy are progressive as the GFR falls and CKD worsens. This though anemia is a major hematological challenge in CKD, coagulation abnormalities also exist and complicate management further.

Anemia was first linked to renal disease by Richard Bright in 1836 who is known as father of Nephrology. The anemia of CKD is highly associated with adverse outcomes such as cardiovascular events and increased mortality. Erythropoietin and iron deficiency, blood retention in the dialyser, gastrointestinal bleeding all would contribute to anemia. Restoration of normal hematocrit by iron, darbepoietin alfa and human recombinant erythropoietin reduces requirement for blood transfusion and decrease cardiovascular mortality by 30%. This hematological aspects of CKD composed a significant perspective in the management and outcome of chronic kidney disease.

Aim

To correlate hematological indices of anemia in ESRD and coagulation with cardiac function.

MATERIALS AND METHODS

Study Place

Dhanalakshmi Srinivasan Medical College and hospital, Siruvachur Perambalur.

Study Population

All patients who presented for renal transplantation as recommended by urologist and nephrologist.

Study Period

Jan 25 to March 25.

Study Sample

25 cases.

Study

Retrospective observational study.

Study Parameters

Hemoglobin, PCV, RDW, INR, platelets, Ejection fraction, RVSP, LA diameter, along with serum creatinine.

Methods

The case records, laboratory and echocardiogram reports of the patients who attended the preanesthetic clinic were scrutinised and the selected aforesaid parameters were noted. The results were tabulated and analysed.

RESULTS

Hemoglobin, red cell width and platelets showed negative correlation with r value of -0.015 with creatinine levels. A lower hemoglobin and PCV was associated with poor ejection fraction (p=0.01) and raised RVSP (P=0.05). The values of ejection fraction and PCV showed p= 0.011, red cell width vs RVSP depicted p= 0.076, packed cells with EF showed p = 0.011, LA diameter with ejection fraction showed p= 0.004. Hemoglobin and ejection fraction showed a significant p value = 0.007.

Creatinine Levels by Gender

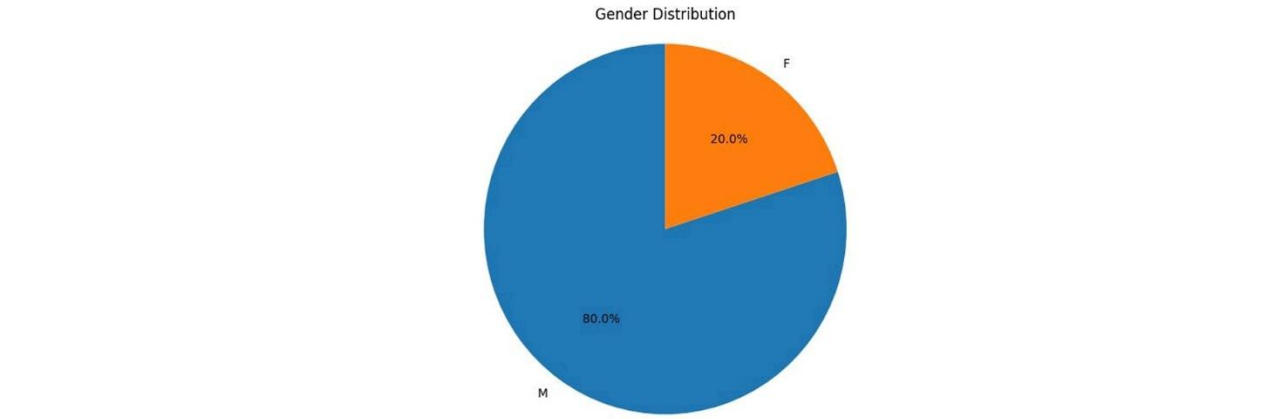

Figure 1: Gender Distribution among Study Population

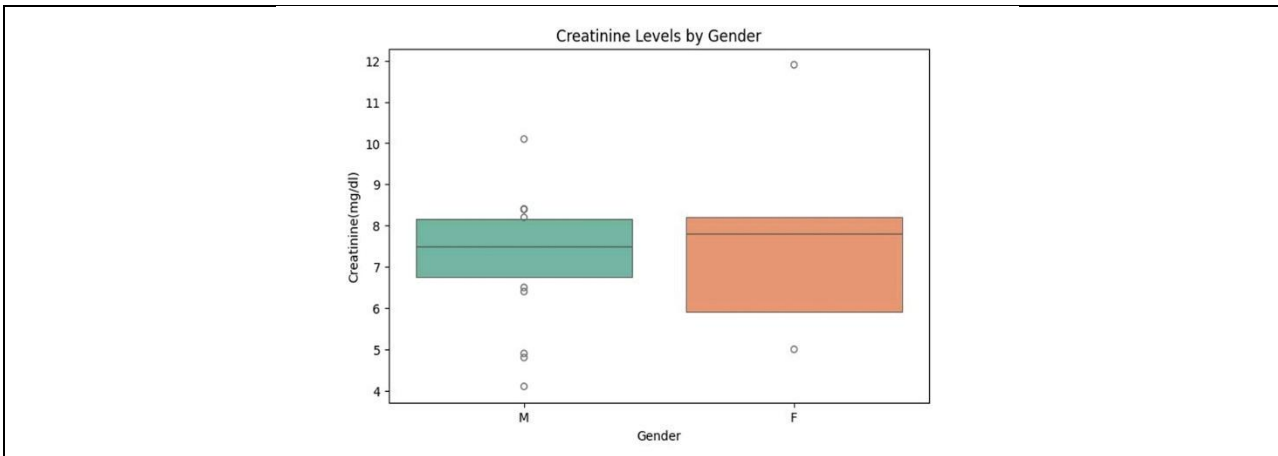

Figure 2: Creatinine Levels by Gender

80% of our study population were males and 20% females. Creatinine levels ranged from 4-12 mg % with most males in 7-8 mg% and most females with creatinine between 6-8 mg %.

Distribution of Hb Levels

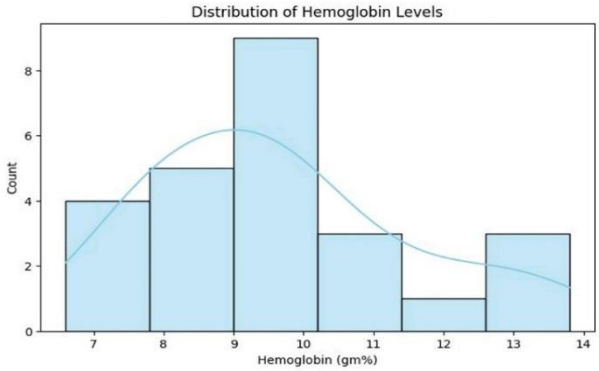

Figure 3: Distribution of Hemoglobin among Study Population

The hemoglobin values in the study group from 6g% to 13 g% with more than 8 patients in 9-10g% group. Scatter plot between hemoglobin and packed cells volume:

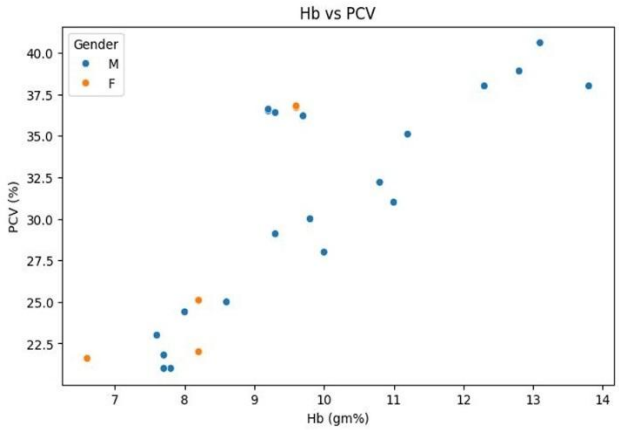

Figure 4: Scatter Plot between HB and PCV

As all the patients were posted for renal transplantation they had been dehydrated by dialysis and hemoglobin greater than 10g% is a post transfusion value. As per the diagram Hb and PCV are proportional to each other.

Binary Comparison of Parameters as Scatter Plots

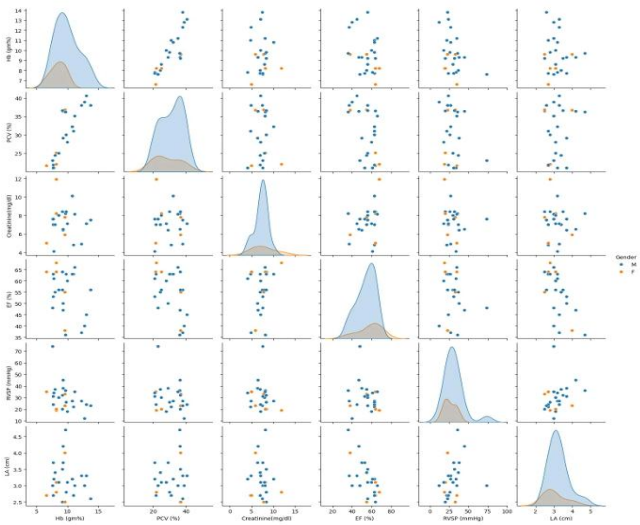

Figure 5: Binary Comparison of Parameters as Scatter Plots

Each parameter is plotted against all the other parameters and depicted as diagram. Here we see grouping of the values of for example hemoglobin against right ventricular systolic pressure where a

hemoglobin less than 9 g% has RVSP upto 40 mmHg. Thus pulmonary hypertension is evident with anemia. Serum creatinine between 5-9mg/dl show left atrial diameter between 3-4.5 cm and ejection fraction less than 50%. This diagram also shows the distribution of the parameters.

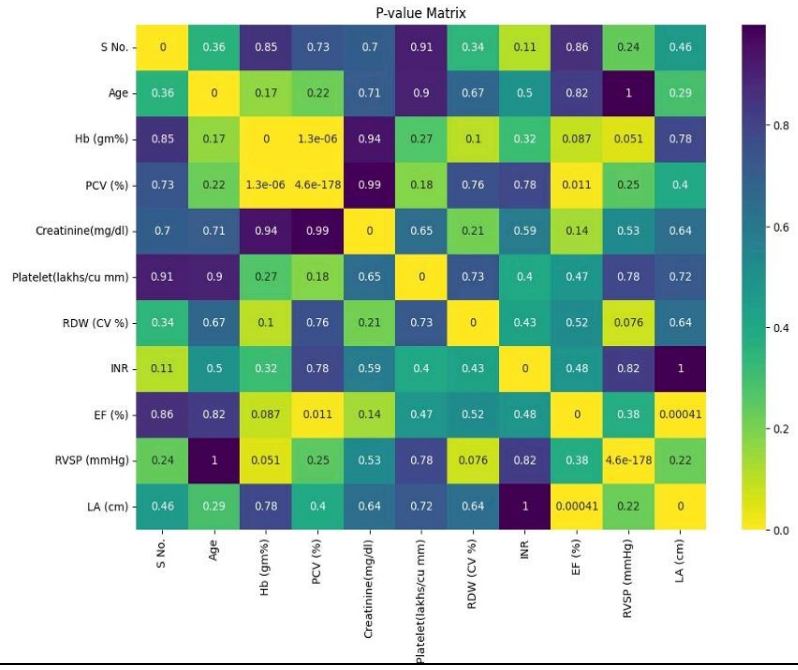

Figure 6: P Value Matrix

P value matrix which is computerised calculation of p value of every parameters against the other and the value of the centre of the each box. Yellow to yellowish green shades are significant while dark blue/black is statistically insignificant. PCV to platelets has p of 0.18 and PCV to ejection fraction p = 0.011. INR to RDW is 0.43.

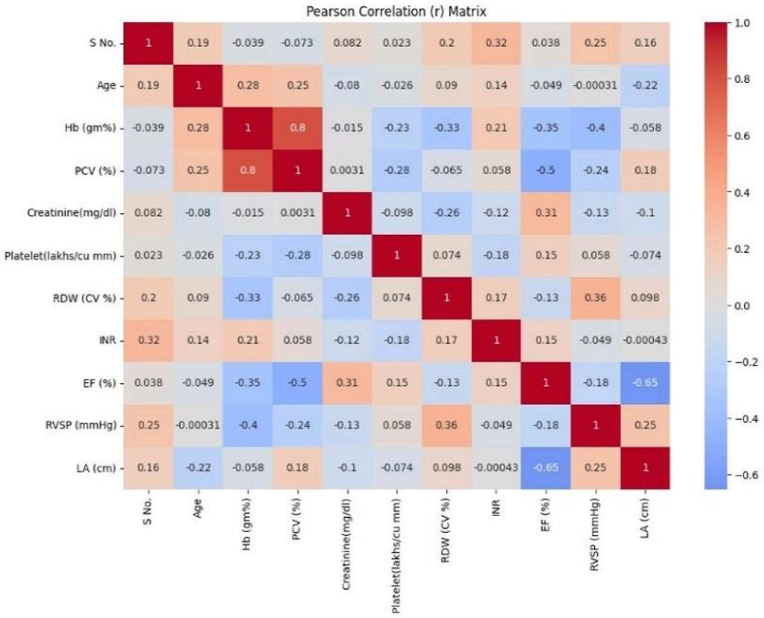

Figure 7: Pearson Correlation Matrix

Figure 10 Is the Pearson correlation matrix depicting r values. Where pale to bright red close to a value of one are significant. RDW and Creatinine have correlation of 0.2 Hb and RDW have negative correlation (that is inversely proportional) with r of -0.33.

DISCUSSION

Erythropoietin plays a central role in the regulation of erythropoiesis. Anemia is defined as reduced erythrocyte mass which may be due to loss or reduce production or impaired stages of erythropoiesis leading to increased destruction. As direct measurement of erythrocyte mass is cumbersome, hemoglobin and hematocrit values are utilised for definition and analysis. The reduced red cell mass results in reduced oxygen carrying capacity and delivery of oxygen to body tissues and organs.[1]

Hematopoiesis proceeds through three different stages from early embryonic life namely the mesoblastic stage in yolk sac, hepatic stage and myeloid stage.[2] Primitive hematopoiesis begins in extraembryonic yolk sac during 3rd week of embryonic life, this transient phase has nucleated erythroid cells namely megaloblasts that contain embryonic Hemoglobin. Gower I, II and portland hemoglobin are the embryonic hemoglobin types. Definitive hematopoietic stem cells arise subsequently intra embryonically at the site of dorsal aorta called the aorta gonads mesonephros (AGM) region. These stem cells migrate to the liver, spleen, bone marrow and liver and spleen become the main sites of hematopoiesis from 2 to 7 months.

Endothelial dysfunction is the basic pathology of several inter related disorders such as preeclampsia, chronic renal disease and hypertensive disorders. Recent evidence indicate that hemopoietic cells and endothelium originate from common precursor called hemangioblast. The bone marrow starts blood cells production around 3rd to 4th month and by birth it becomes an exclusive site of hemopoiesis.[3]

The whole process of erythropoiesis is result in a red cell production rate such that the red cell mass in the body stays constant. The glycoprotein erythropoietin has been established as the major humoral regulator of red cell production. Erythropoietin (Epo) was originally purified from the urine of patients with aplastic anemia. It has a molecular weight of 34000 Daltons and contains 30% carbohydrate of which 11% is sialic acid, 11% total hexose and 8% N- acetylglucosamine. The potency of the purified human urinary EPO has been determined to be 70,400 U/mg of protein or 50,000 U/mg of total weight. The gene encoding has been localised on human chromosome 7 (7pter-q22). The EPO gene exists as a single copy in a 5.4 .kb DNA fragment and contains fours introns and five exons for 193 amino acid peptide. It includes a 47 amino acid signal peptide (leader sequence) anda 166 amino acid peptide with MW 18,398. The human EP has four cysteine residues linked by disulphide bonds which when reduced or alkylated, lead to significant loss of activity. Recombinant EPO is highly glycosylated with MW 30,000 and contains 39% carbohydrate. Glycosylation of the hormonal peptide is absolutely necessary for its invivo activity.the new product darbepoietin is a novel erythroid stimulating protein. It is highly related to EPO and binds to same receptor but has longer invivo life.[4]

Almost 59 years ago Jacobson et al established that kidney is the major organ of EPO production in adult rats.[5] Human with end stage renal failure were found to have low serum EPO concentrations which were restored to normal after successful renal transplantation.[6] After experimental bleeding in mice EPOmRNA in kidney increase 500-1000 times compared to normal kidney. 7% of the total EPO mRNA is produced by liver specialised cells producing EPO have been identified in hepatic and renal parenchyma by the technique of in situ hybridization using radioactive probes specific for EPOmRNA. These cells are found in the interstitium of renal parenchyma outside the tubular basement membrane mostly in the inner cortex and outer medulla. These cells are fibroblast like type one interstitial cells. EPO is synthesised de novo in response to hypoxia. The EPO gene contains sequences that are oxygen sensitive which can confer the ability to respond to a hypoxic stimulus. The ligand for the oxygen sensitive enhancer was identified as a Protein of 120 kd termed hypoxia inducible factor-1. This appears to be the physiologic regulation of EPO transcription.

HIFs are heterodimers, helix loop helix, transcription factors with two subunits HIF-1α and HIF-1β. HIF-1α is constitutively expressed under normoxic conditions but rapidly degraded via the ubiquitin proteosome complex after it is tagged with the protein of vonhippel lindau. Binding of the protein to HIF-1α requires hydroxylation by a proline hydroxylase which is an oxygen and iron dependent enzyme.[7] Asparaginyl hydroxylase is another oxygen sensitive enzyme involved in regulating EPO production.

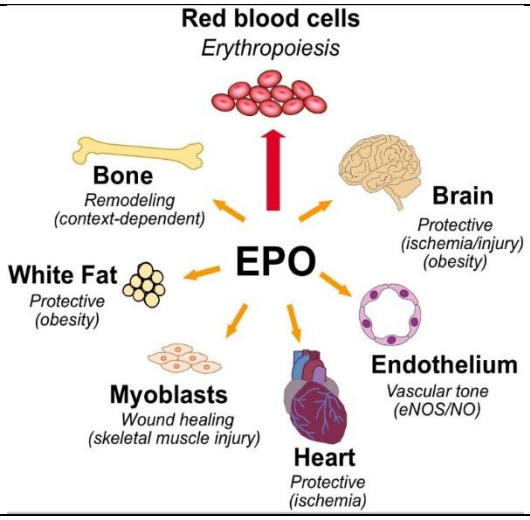

Figure 8: Functions of Erythropoietin

EPO is a hormone that promotes erythroid differentiation. The role of EPO during early stages of erythropoiesis is undefined. The erythroid cells that is the most sensitive to EPO is a cell between CFU-E and proerythroblast. These cells express the highest density of EPO receptors on their membrane and are absolutely dependent on EPO for survival. Animal studies have shown that the binding of EPO is followed by a series of biochemical events including increase in calcium uptake, internalisation of the hormone, increase in total RNA synthesis, glucose and iron uptake,[8] espression of transferrin receptors and eventually increase of hemoglobin synthesis as well as of membrane bands 3 and 4.1, increased rate of erythroid differentiation, ending with increase in reticulocyte count and finally an increase in red cell mass. In the absence of EPO erythroid cells die. The pattern of rapid DNA clevage occuring in erythroid cells deprived of EPO is characteristic of cells undergoing apoptosis or programmed cell death.[9] In addition to erythroid cells,EPO affects megakaryocytes and their progenitors. Though platelet count is unaffected by EPO deficiency platelet dysfunction occurs. Extensive homology exist between EPO and thrombopoietin which is the major humoral regulator of platelet mass.[10]

HIF-2 is specifically involved for hypoxia driven EPO production. In the absence of of HIF-α subunits the hepatic HIF-2 becomes the main regulator of EPO production. HIF-2α and HIF-β, hepatocyte nuclear factor-4 and p300 bind to a 120 bp enhancer which is located at the 3' end of human EPO polyadenylation signal. This interaction results in rapid EPO transcription followed by translation and secretion of EPO.

Anemia in Chronic Disease is anemia that is observed in patients with infections, inflammatory or neoplastic disease that persist for more than one or two months. The characteristic feature of this syndrome is the occurrence of hypoferremia in the presence of ample reticuloendothelial iron stores. The hypoproliferative features predominate in anemia of chronic renal insufficiency resulting from failure of endocrine and filtering functions of the kidney. In polycystic kidney disease, the erythropoietin secreting function of the kidney is apparently preserved even whom filtering function is lost.[11] Erythropoietic activity can be found in the cystic fluid and may arise from single interstitial cells juxtaposed to proximal tubular cysts.

Three factors are involved in the pathogenesis of anemia of chronic renal failure namely erythropoietin deficiency, supression of marrow erythropoiesis and shortened RBC survival.[12] In severe anemia, ferrokinetic studies demonstrate that plasma iron transport rate is normal but red cell iron utilisation and erythrocyte iron turnover are decreased. With milder degrees of anemia, ferrokinetic measurement tend to be near normal. Such normal values indicate insufficient marrow response to anemic stimulus.

Uremic itself suppressed heme synthesis polyamine spermine accumulate in renal failure. Inhibitors of multipotential stem cells growth have also been detected in uremic plasma. Parathyroid hormone associated with secondary hyperparathyroidism in renal failure patients may also contribute to marrow

suppression.[13] Cytokine mediated anemia mechanisms typically associated with anemic of chronic disease may be active in renal failure.

The third pathogenetic factor is hemolysis. 20-70% of uremic patients show shortened red cell survival. The extent to which red cell survival is decreased is related to degree of azotemia. Hemolytic factors are presumed to be a toxic substance normally excreted or metabolised by the kidney. Guanidine and it's derivatives appear to be a subset of many retained metabolites that adversely affect erythrocyte survival. Peroxidation of membrane lipids by free radicals may also contribute to shortened survival.[14] Several abnormalities have been described in uremic erythrocytes that could lead to premature destruction. An abnormal externalisation of phosphatidyl serine, a phospholipid normally present only inside the RBC, has been associated with increased erythrophagocytosis and anemia in CKD.[15] Uremic RBC are more fragile and the rheologic properties are altered owing to changes in RBC shape and decreased deformability. The osmotic stimuli of uremic renders RBSs more fragile. Glutathione deficiency causes the RBCs to have reduced response to oxidative stress. This explains the benefits of dialysis on hematological aspects following hemodialysis where the vitamin E bound dialysis membranes offer antioxidant effect.[16] Carnitine deficiency, abnormal deposition of complement onto erythrocytes in CKD, both have contribution towards reduced survival of erythrocytes but these vary from patients to patient making it extremely difficult to converge, particular deficiency to be identified in anemic CKD patients who may be specifically affected.

Erythropoietin alone has consistently proved to be a causative factor in anemia of CKD as the latter improves on periodic supplementation of erythropoietin. The EPO concentrations are inappropriately low for the degree of anemia. The adequacy of EPO production in response to anemia appears to decline in rough proportion to the degree of reduction in nephron mass. In patients with creatinine clearance velo40ml/minute, mean serum EPO concentrations were severely depressed. The peritubular fibroblasts responsible for EPO production are transformed into myofibroblast leading to reduced EPO production. The pharmacological stabilisation of hypoxia inducing factors (HIF) with inhibitors of prolyl hydroxylase results in significant secretion of EPO from renal and extrarenal tissues. The peritubular fibroblasts found located in the renal cortex have been suggested to be derived from neural crest and share characteristic of pericytes.[17]

The quantity of EPO is traditionally expressed in units with 1 unit representing the same erythropoietic effect in animals as occurs after stimulation with 5mmol cobalt chloride steady state production of small amounts of EPO maintains the serum EPO concentration at 10-30 units/litre enough to stimulate sufficient production of erythrocytes to replace those lost to senescence.[18] When anemia or hypoxia is present, serum EPO concentration increase rapidly to as much as 10,000 units/litre.

In aplastic anemia the EPO values remain elevated. Differentiation of hemopoietic stem cells (HSCs) to erythrocytes is dependent on erythropoietin which is necessary for survival and continued differentiation of erythroid lineage committed progenitors colony forming unit-erythroid cells (CFU-E). Classically the development of RBCs from HSCs is a multistage process that progresses through multipotent progenitors (MPPs) and common myeloid progenitors (CMPs). The latter gives rise to bipotent megakaryocytes -erythroid progenitors (MEPs) from which unipotent erythroid progenitors burst forming unit (BFU-E) cells. The formation of BFU-E from MEP and their conversion to CFU-E is erythropoietin dependent early erythropoiesis. This is followed by terminal erythroid differentiation (TED). The transition of CFU-E to proerythroblast marks the onset of terminal erythroid differentiation which advances along proerythroblast, basophilic erythroblast, polychromatic erythroblast and orthochromatic erythroblast which forms reticulocytes that ultimately mature into erythrocytes.

These the existence of platelet dysfunction hand in hand with anemia in end stage renal disease is explained by the common progenitors to platelet and red cell namely the megakaryocytes erythroid progenitors which is dependent on erythropoietin for erythroid differentiation. Iron metabolism and it's regulation deserve next to be discussed as their affection in CKD has opened up therapeutic opportunities.[19]

Patients with CKD are in negative iron balance due to increased blood loss. Excessive bleeding is a significant complications of CKD. Coagulopathy, occult blood loss by gastrointestinal bleeding, blood

loss due to dialysis (1-3L/year) and clinical laboratory testing procedures. Each millilitre of blood contains approximately 0.5mg of iron reasoning iron deficiency following blood loss. In the absence of chronic inflammation, blood loss leads to reduction in serum ferritin and serum iron values and a progressive increase in the desaturation of transferrin, below 16% threshold that guarantees normal supply of iron to the erythroid marrow. Reduced intestinal absorption of iron in patients on maintanence dialysis was noted due to concomitant inflammation.

Hepcidin is a 25 amino acid peptide produced and secreted by the liver modulates iron availability by promoting internalisation and degradation of ferroportin a key iron transporter that is essential for iron absorption in the duodenum and recycling of iron or iron efflux by macrophages.[20]

Hepcidin concentrations are high in iron overload states and decreased in iron deficiency states. High hepcidin concentrations turn off both duodenal iron absorption and release of iron from macrophages. Low hepcidin promotes iron absorption and heme iron recycling and iron mobilization from macrophages. Erythroferrone has been identified as the key mediator of erythropoietic regulation of iron metabolism. Urinary and serum concentrations of hepcidin have been measured with mass spectrometry. Normal range of serum hepcidin is 29 to 254 ng/ml in men and 16-288ng/ml in women. Residual kidney function, iron stores, erythropoiesis status and inflammation all seem to be related to hepcidin concentrations observed in CKD. Another regulator of iron homeostasis, is growth differentiation factor 25 that is induced by hypoxia and iron depletion and down modulates hepcidin thus contributing to.

Iron overload in condition with significant expansion of bone marrow and inefficient erythropoiesis. Folic acid, vitamin D and zinc deficiency also occur hand in hand with iron deficiency. A net loss of folate is associated with dialysis. Changes in RBC parameters are helpful in identifying folate deficiency such as in MCV and MCH.

Hemoglobin denotes the oxygen carrying capacity of the red cell mass oxidative stress to the bone marrow suppresses erythropoietic response to anemias. Maturation of RBC are interfered with defective production of colony forming units which is an erythropoietin dependent process. More over the cofactors needed in the maturation of RBC such as iron and folic acid have defective absorption from gut leading to anemias. The packed cells volume depicts the red cell mass independent of fluid overload that is often seen in ESRD.

Red blood cell analytical parameters include blood counting procedures and red cell indices. The blood counting procedures include counting of red Cells, White cells, platelet and reticulocytes. Red cell indices are hemoglobin concentration, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration. Red cell width distribution is a red cell measurement that quantitates cellular volume heterogeneity reflecting the range of red cell sizes within a sample.[21] RDW becomes abnormal earlier in nutritional deficiency anemias than other red cell parameters. RDW is particularly useful in characterising microcytic anemia, allowing to distinguish between uncomplicated iron deficiency anemia (high RDW, normal to low MCV) and uncomplicated heterozygous thalassemia (normal RDW, low MCV). RDW is useful in identifying red cell fragmentation, agglutination in dimorphic population including patients who had transfusion, sideroblastic anemias or have recently been treated for a nutritional deficiency.[22]

INR is often raised when there is a super added hepatorenal syndrome and the sample clinical testing is heparinised as in post dialysis state. Platelet dysfunction occurs both with renal disease itself and heparinisation with hemodialysis. Platelet counts are often normal but thrombasthenia or defective platelet adhesion have occurred and identified as the prime case of bleeding in CKD.

Echocardiogram is the routine and non-invasive modality to indirectly identify pulmonary hypertension as right ventricular systolic pressure. Diastolic dysfunction of left ventricle occurs early in the disease followed by recurrence of dilated cardiomyopathy simultaneously with fluid overload which the kidney is unable to handle. The systolic function depicted as ejection fraction ironically is associated with hypertension due to an active renin angiotensin mechanism. The left atrium when enlarged more than 3.8 cm is an indication of both pressure and volume overload thus increasing the incident of congestive heart failure or pulmonary edema.

Aluminium overload: Aluminium was commonly used in patients on dialysis for its effect as a potent intestinal binder of phosphate. Presently calcium and non-calcium containing phosphate binders have replaced aluminium. The erythropoietic effects of aluminium toxicity are altered iron metabolism, direct inhibition of erythropoiesis, disruption of red cell membrane function and rheology. In dialysed patients microcytic anemia is noted which improves with use of deionised water to reduce aluminium content of dialysate or chelation therapy with deferoxamine. Erythropoiesis of patients with CKD include polycystic kidney disease, post transplantation state, renal artery stenosis and renal tumours.

Disorders of Hemostasis in Chronic Kidney Disease include both excessive bleeding and hypercoagulability. Traumatic disruption of the endothelial lining of blood vessels results in a complex response to maintain vascular integrity and prevent bleeding. The first line of defense is platelet which interact with ligands such as collagen, fibronectin, laminin, thrombospondine and von willebrand factor – which are exposed on a consequence of endothelial damage. The adhesive ligands further promote activation by releasing aggregating agents such as TXA2 and ADP. The surface of platelets play essential role in supporting coagulation cascade in the plasma and thus enters common pathway. The limitation to coagulation is by nitric oxide and prostacycline. Tissue factor pathway inhibitors, protein C and protein S system and antithrombin are further limitation to coagulation. Fibrinolytic system too limits the growth of thrombi. Fibrin digestion is mediated by plasma which is formed by activation of plasminogen by tissue plasminogen activator.

Bleeding in uremic patients occurs despite normal or elevated circulating values of coagulation factors. Platelet abnormalities are the primary cause of bleeding diathesis. The function of platelets is impaired whereas the number of circulating platelets is normal. Evidence of platelet dysfunction includes elevated bleeding time, diminished aggregating response to ADP and epinephrine, reduced ristocetin induced platelet agglutination and prolonged closure time with platelet function analyser. The most constant abnormality in platelet function in uremia is impaired interaction of platelet with vascular Endothelial production of nitric oxide appears to increase in uremia leading to higher concentrations of cGMP and reduction of platelet responsiveness. Prostaglandin I_2 released by endothelium is increased in patients with CKD causing increased bleeding times and reduced platelet aggregability.[23]

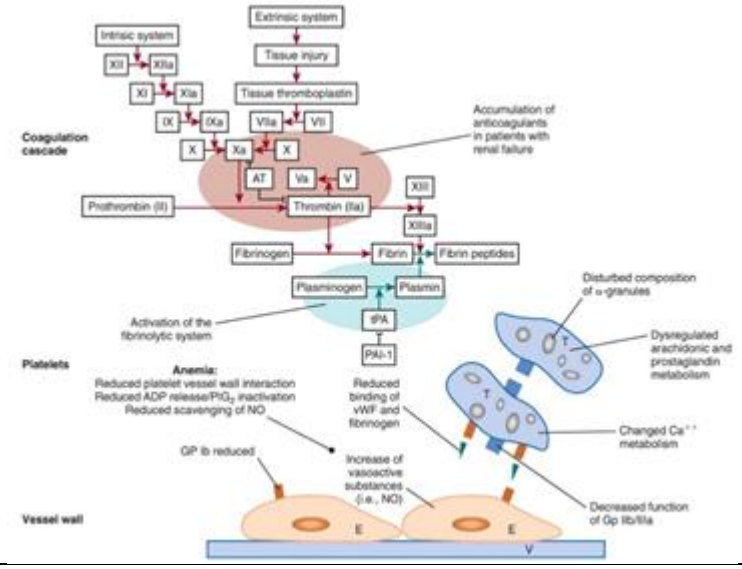

Figure 9: Etiology of Bleeding in Renal Failure

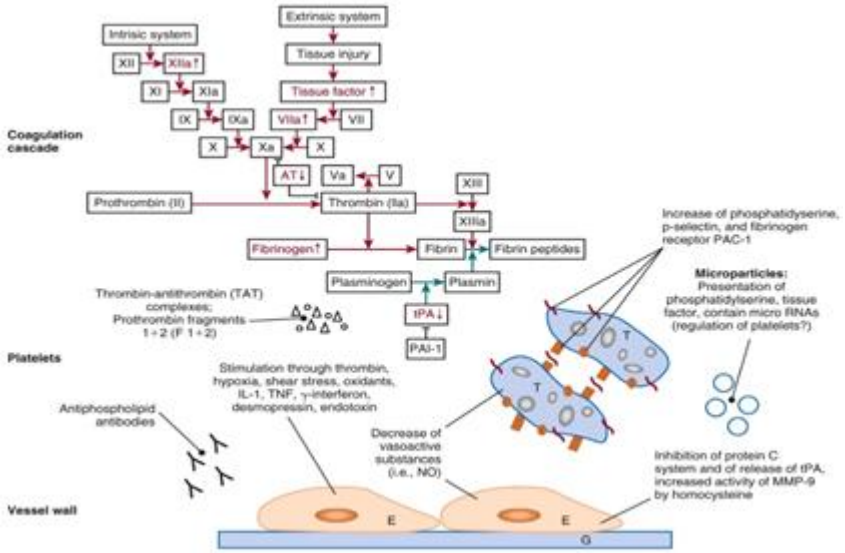

Figure 10: Etiology of Thrombosis in Renal Failure

CONCLUSION

End stage renal disease projects significant involvement of several systems especially cardiac and hemopoietic system.

The erythropoietin production from peritubular fibroblasts in the kidney appears to be directly proportional to the glomerular mass. Anemia, bleeding and thrombogenicity co-exist in ESRD. Increased tendency to bleeding is appears mostly due to platelet dysfunction. Early erythropoiesis is erythropoietin dependent where later phases of erythropoiesis are independent of the cytokine hormone. An increase in red cell width distribution was associated with severity of anemia. A low Hemoglobin and packed cells were associated with increased right ventricular systolic pressure (p=0.05) but poor ejection fraction (p= 0.01).

Through the early cardiac changes in renal disease have been discussed as change in left ventricular geometry there is no early echocardiographic changes in left ventricle. Anemia of uremia is consistently associated with pulmonary vascular Endothelial dysfunction evaluated as right ventricular systolic pressure by echocardiogram. Hemostasis problems are more due to platelet dysfunction than erythropoietin reduction. Anisocytosis depicted as increase in red cell width distribution indicate co existing hemolysis consistent with rise in creatinine levels. Hemopoiesis and hemostasis are both affected in end stage renal disease. Leukodepleted red cell transfusion, erythropoietin supplements may help in improving myocardial oxygenation thereby reducing cardiac morbidity and mortality.

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