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REVIEW ARTICLE

Anemia in Diabetic Kidney Disease

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Introduction

Diabetic kidney disease is an important cause of kidney disease in our country.[1] CKD is defined as impairment of kidney function of greater than or equal to 3 months duration characterized by either (i) fall of Glomerular filtration rate (GFR) less than 60 ml/min or (ii) if GFR is more than 60ml/min there should be other markers of kidney damage such as presence of proteinuria, hematuria, shrunken kidneys or fibrosis on biopsy.[2] CKD has 5 stages based on GFR and urine protein criteria. In Stage 1, there is evidence of kidney damage but GFR is preserved (>90 mL/min). Stage 2 is mild kidney damage with GFR 60–90 mL/min; Stage 3 is moderate kidney damage with GFR 30–59 mL/min; Stage 4 is severe kidney damage with GFR 15–29 mL/min while Stage 5 is end stage renal disease (ESRD) with GFR <15 mL/min. Patients in Stage 5 are often treated with dialysis or kidney transplantation.

Anemia of DKD

Anemia is an important complication of CKD. Anemia has been defined by the World Health Organization (WHO) as a hemoglobin (Hgb) concentration <13.0 g/dL for adult males and postmenopausal women and an Hgb<12.0 g/dL for premenopausal women.[3] Based upon these criteria, nearly 90 percent of patients with a glomerular filtration rate (GFR) <25 to 30 mL/min have anemia, many with Hgb levels <10 g/dL.[4] The prevalence of anemia increases with higher stages of CKD.

Although the prognosis with diabetic nephropathy has improved since early reports there remains an excess mortality of 70 - 100 times that of an otherwise matched population.[5] In diabetic patients anemia is seen not only in preterminal renal failure, but also frequently in patients with only minor derangement of renal function.[6] Patients presenting with diabetic nephropathy commonly have a greater degree of anemia for their degree of renal impairment than those presenting with other causes of renal failure, and anemia develops earlier in these patients than in those with renal impairment from other causes.[7]

In a study, for each CKD stage, haemoglobin was 1 g/dl lower in patients with diabetes than in the non-diabetic population.[7]

Anemia leads to worsening of symptoms of CKD. Anemic patients have easy fatigability, loss of exercise tolerance, loss of libido and decreased appetite. The hyperdynamic circulation caused by anemia may result in congestive cardiac failure, cardiovascular morbidity and mortality.[7]

Causes of Anemia

Anemia in CKD may be multifactorial. (Table 1) [9,10]

The important causes of anemia in CKD are

(i) Nutritional anemia- it results from deficiency of iron, folic acid or Vitamin B12. Poor appetite, impaired absorption due to oedema of the gut wall, interaction of iron with other drugs in the gastrointestinal tract lumeneg phosphate binders which are commonly prescribed in CKD, alterations in pH of the stomach due to antacids and loss of intrinsic factor required for B12 absorption cause nutritional anemia. Iron deficiency is the most important cause of this type of anemia. Iron deficiency can be absolute or functional. Absolute iron deficiency is characterized by decreased

Table 1 | Causes of anemia in DKD			
Iron deficiency	Absolute iron deficiency	Low ferritinLow TSAT	Supplement ironLook for blood loss
	Functional iron deficiency	High ferritinLow TSAT	Rx inflammation
Erythropoietin deficiency	Decreased Epo production in DKD Resistance to epo action	Normochromic, normocytic anemia Anemia despite adequate Epo • Hyperparathyroidism • Inflammation • PRCA	EPO Rx cause
Hemolysis	Accelerated hypertension, drugs, hemoglobinopathies	High LDH, Low haptoglobin, high bilirubin	Rx cause
Vitamin B12 deficiency	Poor nutrition, IF defect	B12 levels	B12
Folic acid deficiency	Poor nutrition	Serum and RBC folate	Folic acid
Factors specific to DKD	Autonomic dysfunction BM thickening ACEi/ARB use		Rx of DKD
Others	Hemoglobinopathies Malignancy	Hemoglobin electrophoresis	Specific Rx

iron stores while functional iron deficiency is characterized by poor utilization of iron for hemoglobin synthesis despite adequate iron stores. In CKD increased levels of inflammatory cytokines such as interleukin-6 enhance production and secretion of hepcidin, a hepatic protein that inhibits intestinal iron absorption and impairs iron transport from the reticuloendothelial system to bone marrow. (Figure 1,2)

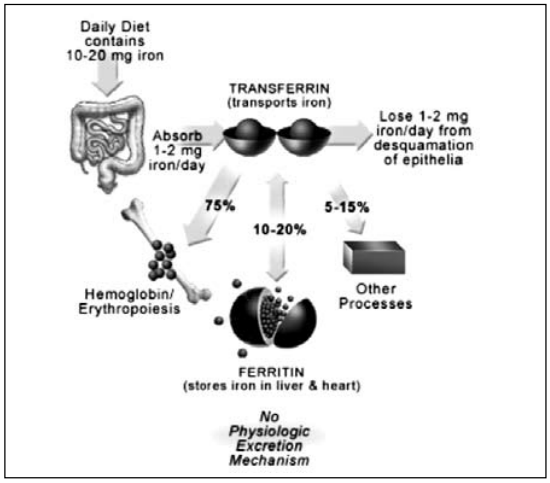

Figure 1 | Iron metabolism

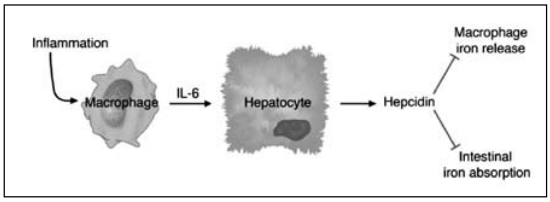

Figure 2 | Hepcidin interferes with iron metabolism

Another cause of iron deficiency in diabetic CKD is that iron excretion increases in early stages of kidney disease in patients with diabetes and albuminuria and is exacerbated by development of nephrotic-range proteinuria.[11,12] In nephrotic syndrome, many nonalbumin proteins are excreted in the urine, including transferrin and erythropoietin. Significant losses of transferrin and erythropoietin can occur in nephrotic syndrome, leading to both iron- and erythropoietin-deficiency–caused anemia in patients with diabetes. Evidence for increased transferrin catabolism in nephrotic syndrome may contribute to iron deficiency–caused anemia.

(ii) Blood loss- CKD patients lose blood during the dialysis sessions. There is also blood loss from gastritis, which is seen in CKD. Thrombastheniaie impaired platelet function contributes to the bleeding tendency in CKD.

(iii) Erythropoietin- Erythropoietin is also known as "Hemopoietine." It is a 30.4 kDa glycoprotein hormone. Primary site of production is liver in the fetus and kidneys after birth. Major sites of production in the kidney is peritubular capillary endothelial cells and peritubular fibroblasts. Actions of EPO include stimulation of erythroid progenitor cells and differentiation of normoblasts to increase the red cell mass in response to tissue hypoxia precipitated by anaemia, haemorrhage, or altitude. (Figure 3)

In CKD there is impaired synthesis of erythropoietin from the peritubular fibroblasts in the kidneys.

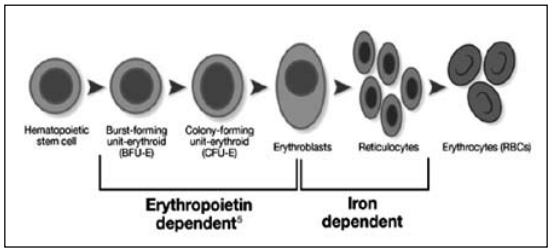

Figure 3 | Mechanism of action of Erythropoietin

The mechanisms of erythropoietin deficiency by diseased kidney include

a. There is a decline in single-nephron sodium absorption. This decreases the O2 consumption, improves oxygenation in outer medulla & decreases the stimulus for EPO production.
b. EPO in circulation neutralized by soluble EPO-R, in dialysis patients, induced by IL-6 & TNF-alpha.
c. EPO inactivated by desialylation, mediated by proteases
d. In bone marrow epoaction blunted by absence of permissive factors like IL-3, calcitriol& CD4 cells, & presence of inhibitory factors like polyamines, ribonuclease& PTH.

(iv) Also uremic toxins lead to resistance to the action of erythropoietin in the peripheral tissues.[13,14] Erythropoietin is a hormone which acts on the bone marrow precursors. Anemia may result from resistance to erythropoietin. Latter results from hyperparathyroidism which causes marrow fibrosis.

(v) Hemolysis is an important cause of anemia in CKD. Hemolysis may be due to hypertension.

(vi) Blood loss is an important cause of anemia in patients with diabetic kidney disease. This may occur due to blood loss from the gastro intestinal tract due to erosive gastritis seen in uremia.

(vii) A major cause of anemia in diabetic kidney disease is an inappropriate response of erythropoietin to anaemia.[13,14]

a. Increased BM thickening
b. Autonomic dysfunction
c. High renin.

(viii) Diabetic patients are on ACE inhibitors (ACEi) or angiotensin receptor blockers (ARBs). These drug classes may cause a reversible decrease in Hb concentration in patients with diabetes and CKD. The mechanisms by which lower Hb include a direct blockade of the proerythropoietic effects of angiotensin II on red cell precursors, degradation of physiological inhibitors of hematopoiesis, and suppression of IGF-I. Long-term administration of losartan in 50- to 100-mg doses once daily in patients with diabetes and albuminuria is expected to lower Hb by <"1 g/dl.[15] Importantly, this effect does not diminish the renoprotective effect of losartan.

(ix) Others- Hemoglobinopathies, malignancies etc may be some other rare causes of anemia.

Laboratory Evaluation of Anemia

Complete blood picture including Hb concentration should be done along with Red blood cell indices (MCH, MCV, MCHC), white blood cell count and differential and platelet count. Absolute reticulocyte count is also essential.

Microcytic anemia is seen in iron deficiency anemia while B12 and folate deficiency are important causes of macrocytic anemia. Erythropoietin deficiency anemia is typically normocytic and normochromic. Iron deficiency anemia can be confirmed by evaluation of iron profile which includes serum iron, ferritin and total iron binding capacity. Transferrin saturation (TSAT) is calculated by dividing serum iron level by iron binding capacity. The recommended iron levels in CKD are >100 ug/dl and TSAT should be > 20%and ferritin >100 ng/ml l. Iron dextran therapy must be discontinued for 2 weeks prior to performing measurements of iron status. With Iron sucrose, iron indices can be checked 48 hours after the last dose.[9,10]

Newer markers of iron deficiency include percentage of hypochromic RBC, hemoglobin content of reticulocyte and serum soluble transferrin receptor, which is upregulated when iron stores are decreased. Stool for occult blood should be done to rule out blood loss from the gastrointestinal tract. Elevated serum lactate dehydrogenase level suggests hemolysis.

A blood film showing oval macrocytes and hypersegmented neutrophils in the presence of an elevated MCV may alert the clinician to the presence of underlying cobalamin or folate deficiency. Cobalamin and folate assays should be assessed concurrently due to the close relationship in metabolism.

A serum cobalamin cut-off level of either 148 pmol/L (200 ng/L) or one derived from a local reference range should be used as evidence of cobalamin deficiency in the presence of a strong clinical suspicion. Elevated plasma homocystine and/or plasma Methyl Malonic acid levels, depending on availability, may be considered as

supplementary tests.

A serum folate level less than 7 nmol/L (3 µg/L) is indicative of folate deficiency. Routine red cell folate testing is not necessary since serum folate alone is sufficient in most cases but may be done in the presence of strong clinical suspicion of folate deficiency, despite anormal serum level, a red cell folate may be undertaken, having ruled outcobalamin deficiency. Plasma tHcy can be measured to confirm suspected folate deficiency only in special circumstances; a level above 15 µmol/L could be indicative of folate deficiency.

Effects of anemia in CKD- Anemia causes hyperdynamic circulation and tachycardia, may precipitate congestive heart failure and is associated with increased risk for cardiovascular morbidity by causing left ventricular hypertrophy. There is a 53% increased risk of mortality in children with hematocrit less than 33% at initiation of dialysis. Anemia may have a role in CKD progression. Low hemoglobin leads to impaired physical activity, increased fatigability, loss of appetite, loss of libido & poor quality of life and increases the risk of hospitalization. Many of the symptoms of CKD may be attributed to anemia.

There is renewed evidence of anemia in diabetes contributing to retinopathy, neuropathy, diabetic foot ulcer, hypertension, stroke, progression of kidney disease, cardiovascular events and mortality.[16-23]

Anemia induced renal hypoxia upregulates hypoxia-inducible factor-1α, a transcriptional regulator of the erythropoietin gene as well as heme oxygenase, nitric oxide synthases, extracellular matrix, and apoptosis genes. It is upregulated by renal hypoxia and induces collagen gene expression in renal fibroblasts, thereby increasing interstitial fibrosis. Anemia may also increase renal sympathetic nerve activity, resulting in increased glomerular pressure and proteinuria (which in turn may accelerate progression of kidney disease), and contribute to worsening kidney function by exacerbating underlying heart failure—a common complication in patients with diabetes and kidney disease.[24]

Treatment

Most common cause of anemia is iron deficiency and erythropoietin deficiency. Hence the treatment is primarily directed to these two conditions. However other causes should be looked for and treated. Standard initial therapy for patients without neurological involvement is 1000 microg intramuscularly (i.m.) three times a week for two weeks. Maintenance treatment for patients presenting without neurological deficit is with hydroxocobalamin 1000 microg im. every three months. In patients with serum cobalamin levels of 'subclinical deficiency' on two occasions, an empirical trial of treatment with oral cyanocobalamin (50 microg daily for four weeks) should be given. Folate deficient megaloblasticanaemia 5 mg of folic acid daily is taken for 4 months and up to 15 mg daily for 4 months in malabsorptive states.

Iron deficiency can be corrected by iron supplementation. If iron indices indicate absolute iron deficiency (TSAT≤20 percent and serum ferritin <200 ng/mL), a sufficient amount of iron to correct the iron deficiency should be administered.[25]

In addition, among patients in whom an increase in hemoglobin concentration is desired, a sufficient amount of iron should be administered to achieve a TSAT near 30 percent, providing the serum ferritin remains ≤500 ng/mL.

Dose is calculated by formula (Desired Hb - actual Hb) × Wt X 2.5 + iron depot

Iron depot- 500mg or 35 mg/kg in children. Approximately 1000 mg of Iron are needed.

Types of preparations

Oral iron supplements are less effective in CKD as these are not absorbed effectively due to gut wall oedema. Also acidic pH is required for iron absorption and the pH gets altered in CKD due to use of antacids and proton pump inhibitors. High doses of oral iron may be needed. Oral iron preparations include iron fumarate and sulphate. Iron fumarate has the highest elemental iron. The dose of elemental iron is 6mg/kg which is higher than the usual iron dose. Iron sulphate is the other preparation commonly available.

Parenteral iron is recommended in most of the CKD patients. Many preparations are available which include iron dextran, iron sucrose, sodium ferric gluconate, ferumoxytol and iron carboxymaltose,

First generation Iron dextran has significant adverse effects including anaphylaxis. Iron dextran protocol consists of the administration (over five minutes) of 25 mg of iron dextran mixed in 50 mL of normal saline as a test dose, with appropriate precautions for treatment of an anaphylactic reaction. If tolerated, larger doses of iron dextran (up to 500 to 1000 mg) may subsequently be given as a slow, intravenous infusion over 4-6 hours. It is not necessary to premedicate patients prior to the test dose, but emergency medications (eg, epinephrine, diphenhydramine, and corticosteroids) must be readily available.

Second generation, nondextran IV irons, such as iron sucrose and sodium ferric gluconate, do not contain dextran, or modified dextran, but they have significant dosage and administration rate limitations. They are characterized by a risk of adverse reactions called labile iron reactions at higher doses which may include hypotension, cramping, diarrhea, or chest pain. Sodium ferric gluconate complex is given as 125 mg over 10 minutes. Eight doses are given over 8 weeks to achieve 1000 mg dose. A test dose is not needed. Iron sucrose is administered by intravenous push over five minutes or by intravenous infusion over 15 to 30 minutes; a test dose is not needed. Usually given as 100 mg over 10 doses over 10 weeks. Iron sucrose can also be administered as an intravenous infusion containing 200 mg of iron over two hours, and subsequent doses may be given at 48-hour intervals until the desired dose of iron has been achieved.

Ferumoxytol was designed with a modified dextran shell to reduce immunogenic potential, but anaphylaxis in individuals with previous hypersensitivity to iron dextran has been reported. For ferumoxytol the manufacturer recommends an initial 510 mg dose, to be followed by a second 510 mg injection three to eight days after the first dose.

Ferric carboxymaltose (FCM), a novel IV iron, is a stable Type I polynuclear iron (III) hydroxide carbohydrate complex. Due to its structure, FCM is more stable than sodium ferric gluconate and iron sucrose. It is therefore possible to administer much higher single doses over shorter periods of time than sodium ferric gluconate or iron sucrose. In addition, it is not a dextran or modified dextran so the risk of hypersensitivity reactions is reduced.

For iron carboxymaltose 15 mg/kg single dose can be given undiluted (max 1000mg) by IV injection (100mg/min) or it can be given as infusion (with 250ml NS only) over 15 minutes. Ferric carboxymaltose in other studies was administered as an intravenous bolus (containing 500 mg elemental iron) or intravenous infusion over 30 minutes (containing 1 g of elemental iron) Test dose is not needed.

Side effects of Iron therapy

Oral iron is associated with gastrointestinal side effects while IV iron may be associated with anaphylaxis and risk of infections. IV iron may also be associated with oxidative stress, inflammation, cardiovascular disease and immune deficiency. Hemosiderosis is characterized by iron overload with deposition of iron in the reticuloendothelial system throughout the body especially in the liver resulting in organ dysfunction.

Other micronutrient deficiencies ie folic acid and vitamin B12 deficiency should be corrected. Any sources of blood loss from GIT should be identified and corrected.

Erythropoietin stimulating Agents (ESA)

In CKD Erythropoietin stimulating agents are indicated to correct anemia. These act by stimulating erythropoiesis in the bone marrow.

Pre-requisites before ESA therapy

All correctable causes of anemia should be treated prior to initiation of ESA therapy. Iron should be repleted before ESA initiation.

Types of ESA

The recombinant human erythropoietins include Epoetin alfa and epoetin beta (different only in glycosylation. These are first generation ESAs and typically have shorter half-lives, requiring frequent dosing 1 to 3 times weekly. Darbopoetin alfa, considered 2nd generation ESA, has been modified from EPO to give it a longer half life and typically can be administered once weekly or once every two weeks. A third generation ESA that is modified from EPO by insertion of a large pegylation chain to make it longer acting, called continuous EPO receptor activator (CERA) is longer acting. The action of CERA on the EPO receptor is different from the other ESA, giving it a much longer half life and typically can be administered once every two weeks or once every month.

Dose of ESA

Dose of Erythropoietin alpha and beta is 20-50 IU/kg per dose three times per week. Long acting ESAs are Darbepotein alfa and CERA. Darbepoietin is used in a dose of 0.45 µgm/kg per week or 0.75 µgm/kg every 2 weeks. Dose of CERA is 100ug per month initially then 50ug per month. These can be subcutaneous or IV.

Hemoglobin targets

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines suggested that ESAs not be started among adult nondialysis CKD patients with Hgb concentrations ≥10 g/dL. For CKD patient with Hgb <10 g/dL, the decision to start ESAs should be individualized based upon the rate of fall in Hgb concentration, prior response to iron therapy, risk of needing a transfusion, the risks related to ESA therapy, and the presence of symptoms. ESAs should not be used to maintain Hgb concentrations >11.5 g/dL, however, individualization of therapy is

necessary as some patients may have improvements in quality of life at Hgb ≥11.5 g/dL and will be prepared to accept the risks. The KDIGO guidelines recommended that ESAs not be used to maintain Hgb ≥13 g/dL.[26]

Benefits of ESA include avoiding or minimizing blood transfusions and correction of anemia-related symptoms. Cardiovascular Risk Reduction by Early Anaemia Treatment with Epoetin Beta (CREATE) study showed benefits of maintaing normal levels of hemoglobin.[27]

Harms - ESA use is associated with stroke, vascular access loss and hypertension esp if hemoglobin exceeds 12 gm/dl. Malignancies can be seen.

Following studies have established that very high hemoglobin levels cause increased morbidity and mortality.

Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study showed increased death, stroke, fatal and non fatal MI in high Hb group.[28]

Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT)

Darbepoietin (Aranesp) group showed an increased dialysis rate & hypertension, increased incidence of stroke and thromboembolic events with very high hemoglobin levels, while red cell transfusions were significantly more common in the placebo group.[29]

Pure red cell aplasia (PRCA) is a rare but serious side effect of ESA. PRCA is a very rare condition and occurs due to impurities in ESA. It is characterized by a low RBC count and a low reticulocyte number. WBC and platelet countsare normal. Patient may show antibody to Erythropoietin. Treatment includes correction of anemia by blood transusion, Peginasitide and immunusuppresive drugs ie steroids.

Hemoglobin cycling

Hemoglobin cycling is a recent concept in anemia management. Minor fluctuations above and below the target range may be normal in any setting; however, wide and/or prolonged fluctuations in hemoglobin are usually associated with several internal and external factors that can influence ESA response and hemoglobin stability including the pharmacokinetics of the ESA used. Minimizing hemoglobin variability can have important short- and long-term clinical consequences. In the short run, fewer fluctuations above 12 g/dl may minimize the occurrence of serious cardiovascular events associated with high hemoglobin levels, whereas fewer fluctuations below 11.0 g/dl provide improved symptomatic relief and maximize survival. Variability can be minimized by using longer acting ESAs.[30]

Erythropoietin hyporesponsiveness

The main causes are hyperparathyroidism, chronic inflammation, iron deficiency, other nutrient deficiencies.

Secondary hyperparathyroidism parallels CKD and worsens with its severity. This is due primarily to deficiency in 1–25 vitD3 and elevated serum inorganic phosphate level both of which stimulate parathyroid hyperplasia and increased parathyroid hormone synthesis, a process called secondary hyperparathyroidism. Secondary hyperparathyroidism increases bone turnover, leading to development of bone cysts and marrow fibrosis, impairing bone marrow function and subsequently anemia Secondary hyperparathyroidism, if uncontrolled, can lead to erythropoietin resistance. Therefore secondary hyperparathyroidism must be routinely checked and aggressively treated in CKD patients.

Chronic inflammation

Chronic inflammation is an important cause of EPO resistance in CKD patients. Chronic inflammation resulting from rheumatologic diseases (such as arthritis, lupus), and chronic infections such as hepatitis C, soft tissue and bone infections is associated with increased circulating levels of cytokines including CRP, tumor necrosis factor, interferon gamma, and interleukins, which impair the erythropoietic response. As CRP should be routinely investigated when erythropoietin resistance is suspected and no other cause can be identified. In general, levels of CRP >10 mg/L, suggest significant inflammation. Occasionally doubling the erythropoietin dose may overcome the resistance. If no improvement is achieved with doubling the dose, further increments are not likely to yield significant results. If no cause of high CRP is detected a clotted arteriovenous graft should be removed, when appropriate. If the screen for sepsis is negative and the patient is believed to have a non-infective inflammatory condition, administration of steroids might be considered. Alternatively, such patients should be maintained on regular doses of erythropoietin and periodic red blood cell transfusion.[31]

Adjuvants

As per the current guidelines there is no role for adjuvants like androgens, vitamin C, vitamin D, vitamin E, folic acid, L-carnitine, and pentoxifylline in management of anemia of CKD.

Newer molecules

Certain newer molecules are being used for correction of anemia. These include

- Peginasetide-Peginesatide (Hematide) is a pegylated, synthetic, dimeric peptide that activates the EPO-R but shares no sequence homology with endogenous EPO. So it is unrecognizable to anti-EPO antibodies & therefore could be used to treat PRCA (Pure red cell aplasia). This molecule has a t1/2 of 14-60 hrs, allowing monthly dosing.
- PHI-Under normal circumstance in conditions of good oxygen availability, prolyl hydroxylase enzyme are responsible for the hydroxylation, ubiquitination & degradation of hypoxia inducible factor (HIF). HIF stimulates erythropoietin. I-Prolyl-hydroxylase inhibitors (PHIs) like FG-2216 & FG-4592 are orally active oxoglutarate analogs. These inhibit PHD proteins. These thus mimic a hypoxic stimulus & lead to stabilization of HIF-alfa & Hypoxia response element (HRE) mediated transcription of multitude of genes.
- GATA 2 inhibitors are newer drugs which enhance HIF-1 activity & EPO levels.
- Phosphotyrosine phosphatase SHP-1, also known as Hematopoietic cell phosphatase (HCP) causes BFU-E recovery in cells cultured from ESA-hyporesponsive HD patients.

Blood transfusions- BT should not be given based on Hb level alone , but if needed to relieve symptoms. Indications of BTinclude (i) Acute hemorrhage, (ii) when rapid pre-operative Hb correction is required and (iii) chronic conditions like ESA resistance/ risks of ESA (malignancy, stroke). *RBC transfusions are preferred over BT to minimize risks of transmission of infections.*

Conclusion

Anemia should be looked for in all diabetic patients who have an eGFR <60 ml/min/1. m^2, and anaemic patients should be referred to renal services for anaemia management. Patients with earlier stages of diabetic nephropathy or stable CKD stage 3 should be followed up in primary care or by diabetologists, who can target cardiovascular risk factors and implement strategies to delay progression of renal disease. Iron and erythropoietin deficiency are the major causes of anemia in DKD. Anemia correction improves quality of life and may retard the progression of CKD.

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"You can never be overdressed or overeducated."
— Oscar Wilde