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Anemia in CKD: A Review

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ABSTRACT

Anemia is the major consequence of chronic kidney disease (CKD), which develops early in course of illness. CKD is microvascular complication of Diabetes Mellitus. Pooled study data shows that reduced hemoglobin (Hb) level is associated with decrease in glomerular filtration rate (GFR). This article reviews the complications and treatment options available for anemia associated with CKD. The introduction of erythropoietin (Epo) in clinical practice, more than twenty years ago, completely altered the management of patients with CKD. The successful correction of anemia of CKD has resulted in reduction of associated morbidity and improvement of functionality, exercise tolerance, cognitive function and overall quality of life. With appropriate erythropoietin stimulating agents (ESA) and iron therapy, anemia can be effectively treated, thereby improving the quality of life inpatients with CKD and anemia.

Key word: Erythropoietin, Erythropoietin stimulating agents, Chronic kidney disease, anemia, hepcidin.

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INTRODUCTION

As per WHO "Anemia is a condition in which the number and size of red blood cells, or the hemoglobin concentration, falls below an established cut-off value, consequently impairing the capacity of the blood to transport oxygen around the body". Anemia is an indicator of both poor nutrition and poor health [1].

Anemia is defined as having Hb value below the established cut off defined by the World Health organization. Different defined groups have different cut offs [2]. For adults:

- Men and postmenopausal women Hb<13.0g/dl
- Premenopausal women Hb<12.0g/dl

Many factors and diseases conditions can be the cause of anemia. For e.g. during pregnancy if body cannot meet the increased requirement of red blood cells. Many autoimmune diseases and other conditions may cause body to make proteins that can destroy RBCs, leading to anemia. Heavy blood loss either due to internal or external bleeding may cause anemia. Also, cause of anaemia can be genetic.

In some types of anaemia for e.g. aplastic anaemia, body also doesn't have enough of other types of blood cells, such as white blood cells (WBCs) and platelets. WBCs help body to fight against infections. Platelets help in blood clotting, which further helps in stop bleeding [3].

What cause anemia? [4]

Worldwide iron deficiency is the most common cause of anemia. It can be caused by prolonged negative iron balance, or lesser dietary iron intake or absorption, or not able to meet the increased needs for iron during pregnancy or growth periods and also due to iron losses as a result of menstruation.

- As per WHO approx. 50% of anemia in women worldwide is due to iron deficiency.
- Other important causes of anemia worldwide include nutritional deficiencies (especially folate and vitamins B12, A and C).
- Genetic conditions including sickle cell disease, thalassemia (an inherited blood disorder) and chronic inflammation.
- Infectious diseases particularly malaria, helminthinfections and other infections such as tuberculosis and HIV/AIDS are important factors contributing to the high prevalence of anemia in many populations.

- Anemia is a particularly important complication of malaria in pregnant women. Pregnant women, especially women who are pregnant for the first time, are susceptible to severe anemia.
- Also, anemia is the major consequence of chronic kidney diseases (permanent or partial loss of kidney function).
- Pregnant adolescents are particularly vulnerable to anemia because they have more amount of iron requirements, for their own growth and the growth of the fetus.

One of the most common cause of Chronic kidney diseases is Diabetes. Most frequent complication of CKD is anemia.

CKD associated anemia

Chronic kidney disease is a prevalent condition worldwide and the number of patients affected continues to increase [5]. As per study conducted by National Health and Nutrition Examination Survey (NHANES) III - the prevalence of anemia increases as GFR falls. Data collected in 2007-2010 showed that anemia was twice which was approx. 15.4% as prevalent in people with CKD, as it was in the general population which was 7.6%. The prevalence increased with the increase of stage of CKD, from 8.4% at stage 1 to 53.4% at stage 5.Kidney failure is the most severe form of CKD and the require renal replacement therapy (hemodialysis, peritoneal dialysis, or renal transplantation), many more patients are affected by less severe forms of CKD. The Kidney Disease Outcomes Quality Initiative (KDOQI) defines CKD on basis of glomerular filtration rate (GFR) and divides the disease into five distinct stages [6].

Anemia in CKD is typically normocytic, normochromic, and hypoproliferative.Diabetes is one of the most common causes of CKD. Although patients with diabetes are regularly monitored for a variety of complications, such as neuropathy and nephropathy. Hb concentrations are not frequently routinely assessed. With kidney disease progression, anemia increases in prevalence, affecting almost all patients with CKD of stage 5. This type of anemia leads to reduced quality of life and increased cardiovascular disease, hospitalizations and mortality [7]. Approximately 90% of the erythropoietin is produced by the kidneys. Under normal conditions, hypoxia in the kidney leads to an increase in the production of erythropoietin, which further stimulates erythropoiesis [8]. Kidney further senses increased oxygenation because of the formation of the new RBC’s and decreases erythropoietin production [9]. As functional renal tissue declines in patients with

Chronic kidney diseases, the body is unable to produce adequate amounts of erythropoietin in response to hypoxia in the kidney [8].

Another factor commonly seen in patients is the use of medications in diabetes that adversely affect Hb production. These include biguanides (metformin), fibrates, thiazolidinediones, and ACE inhibitors. In diabetes systemic inflammation associated with microvascular disease leads to the production of inflammatory mediators, like interleukins and tissue necrosis factor. These mediators dulled the effect of erythropoietin on the bone marrow, where erythroid precursors are stimulated [9].

Other factors which further exacerbate anemia in patients with CKD include platelet dysfunction. This leads to an increased risk of gastrointestinal bleeding, 30-60% shortened erythrocyte survival time compared to normal span of 120 days, and hemolysis. In patients receiving dialysis and especially those on hemodialysis, chronic blood in the dialysis tubing and dialyzer after each hemodialysis treatmentalso contribute to decrease in Hb values [10].

Mechanism of anemia induced by CKD

Two crucial factors responsible for red blood cell production from bone marrow are Iron and EPO. Liver hormone hepcidin controls the iron availability, which further regulates dietary iron absorption and recycling of iron via macrophage mean from senescent red blood cells. Hepcidin levels is controlled by several feedback loops, including iron and EPO. In CKD patients (particularly when patient is on hemodialysis), hepcidin levels have been found to be highly elevated, presumably due to reduced renal clearance and induction by inflammation, leading to iron-restricted erythropoiesis. This inhibitory action on EPO production by the kidney may also lead to circulating uremic-induced inhibitors of erythropoiesis, shortened red blood cell lifespan, and increased blood loss [11]. Recent work has identified hepcidin excess as a main contributor to the disordered iron homeostasis and anemia of CKD by impairing dietary iron absorption and iron mobilization from body stores as shown in **figure 1.**

Black and gray arrows represent normal physiology (black for iron and hormonal fluxes, gray for regulatory processes). Colored arrows represent the additional effects of CKD like blue for activation and red for inhibition.

In fig 1, It is shown that reduction in kidney function in CKD leads to reduction in EPO production and this affect the erythropoiesis from bone marrow. Also with increase in uremic inhibitors shortened the RBC's life span.

Impact of anemia

The impact of anemia on patients with CKD is profound. In add it into the well-known symptoms of fatigue, dizziness, and shortness of breath, anemia has been associated with more severe adverse outcomes, such as cardiovascular complications including left ventricular hypertrophy and congestive heart failure. In patients with diabetes, anemia has been associated with a decline in kidney function, which often occurs in patients with diabetes. Hypoxia caused by anemia stimulates the renin-angiotensin-aldosteronesystem and contributes to renal vasoconstriction. These factors further exacerbate proteinuria by increasing protein in the renal tubules in patients with diabetes [9]. Of note, in patients with type-2 diabetes, anemia has been shown to be an independent risk factor associated with the loss of kidney function [12]. In patients with diabetes, anemia can also contribute to the severity of cardiovascular disease and independently increase the risk of retinopathy. Anemia is also thought to hasten the progression of diabetic neuropathy [12]. Other general complications associated with anemia include reduced cognitive function and mental acuity, impaired quality of life, and the need for blood transfusions [13-16].

Correction of anemia has been shown to improve cardiac function possibly by reducing exercise-induced myocardial ischemia [12]. Treatment of anemia associated with CKD has also been shown to result in improvements in exercise capacity; physical performance features such as endurance; energy; and physical mobility [14]. Patient satisfaction increases when anemia is corrected, as evidenced by higher quality-of-life scores, improved sexual function, better cognition, less depression, and better socialization [15]. In non–dialysis dependent CKD patients, stabilization of renal function has been associated with treatment of the anemia of CKD [13]. Finally, treatment of anemia has been shown to reduce hospitalization and mortality rates [16].

As a result of the potentially severe consequences of anemia in CKD, early recognition and management of anemia are imperative. Consequently, monitoring Hb and detecting anemia in patients with diabetes is essential.

Treatment options available

Optimal treatment of anemia due to CKD requires appropriate diagnosis, ESA and iron therapy, and close monitoring of response. The treatment is summarized in **figure 2**.

Where CBC, complete blood count; CHr, reticulocyte hemoglobin; CKD, chronic kidney disease; ESA, erythropoiesis stimulating agent; Hb, hemoglobin; HD, hemodialysis; IV, intravenous; PD, peritoneal dialysis; PO, by mouth; RBC, red blood cells; TSAT, transferrin saturation.

Available options for anemia treatment in CKD are:

- ESA Therapy
- Iron Therapy

Both of them are explained in detail as follows.

- **ESA therapy**

ESAs are used to stimulate erythropoiesis by either directly or indirectly acting on the erythropoietin receptor. Two ESAs available are:

a) Epoetin alfa

b) Darbepoetin alfa

Both are available in US and Canada. In Europe, epoetin beta is also available. Patients not on dialysis or either on peritoneal dialysis are prescribed with epoetin alfa (typically administered once weekly or once every other week), by subcutaneous route so that the dose can be self-administered at home. Patients on hemodialysis are typically receive epoetin alfa three times weekly by the intravenous route at each hemodialysis session.

After ESA therapy, Hb concentrations of patient should be weekly monitored until Hb level is stable, followed by monthly monitoring [17]. Dose adjustments of ESA are made on basis of:

- Hb concentration
- Target Hb range
- Observed rate of increase in Hb
- Clinical parameters of the patient.

ESA doses are generally increased or decreased by 25% no more frequently than once a month. An exception to this rule is when the Hb is increasing and approaching 12 g/dl or when the Hb concentration increases by > 1 g/dl in a 2- week period. In these circumstances, a dose decrease of 25% is recommended.

Previously, during therapy it was practiced to with held ESA, when level of Hb increased too rapidly (exceeded the upper limit of target Hb). And then therapy used to restart at later point of time when Hb declines below lower limit of targeted Hb. However, the practice of holding doses of ESAs can lead to abrupt reductions in Hb concentration, often to concentrations below the target Hb range, a situation known as "cycling." To prevent the cycling of Hb levels encountered when ESA doses are withheld, current practice is to decrease ESA therapy either by reducing the dose or by reducing the frequency of administration [17].

Iron therapy

Patients with CKD who are not receiving dialysis or those on peritoneal dialysis, iron can be given orally or intravenously. Many clinicians initiate oral iron therapy but patients become intolerant or iron deficient while receiving oral therapy. It is cumbersome to administer Parenteral iron in patients with CKD but not yet receiving dialysis as it requires placement of intravenous access and multiple clinic visits to administer the doses [17].

Three intravenous iron products are commercially available in the United States:

- Iron dextran
- Sodium ferric gluconate
- Iron sucrose.

Because of concerns about life-threatening anaphylactoid reactions to iron dextran, it is no longer in use. Adverse effects of intravenous iron can be severe and include hypotension, chills, back pain, nausea, dyspnea, wheezing, chest pain, facial flushing, rash, and porphyria [17].

In non–dialysis-dependent CKD or peritoneal dialysis, larger single doses of iron sucrose or sodium ferric gluconate have been used (e.g., iron sucrose, 300 mg, or sodium ferric gluconate, 250–375 mg infused during 1 hour) [18,19]. In contrast, IV route of iron administration is preferred in patients receiving hemodialysis because it is unlikely that these patients will absorb a sufficient amount of iron to replace ongoing losses that are associated with hemodialysis.

The 2006 KDOQI anemia treatment guidelines state: "There is insufficient evidence to recommend routine administration of intravenous iron if ferritin level is greater than 500 ng/ml." However, others consider the upper safe limit of ferritin to be 800–1,200 ng/ml. The generally accepted upper limit for TSAT is 50% [20].

Once the level of Hb and ESA is stabilized, it is recommended to perform monitoring after every 3 months.

CONCLUSION

CKD is a worldwide prevalent condition, and the number of patients affected continues to increase. The most common cause of kidney disease is diabetes. Anemia occurs early in development of kidney disease and worsens as kidney function deteriorates. Anemia has been associated with substantial morbidity and mortality. With appropriate ESAs and iron therapy, anemia can be effectively treated, thereby improving the quality of life inpatients with CKD and anemia.

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Stages of CKD	Glomerular Filtration rate (GFR)
Stage 1	≥ 90 ml/min/1.73 m
Stage 2	60–89 ml/min/1.73 m
Stage 3	30–59 ml/min/1.73
Stage 4	15–29 ml/min/1.73 m
Stage 5	< 15 ml/min/1.73 m

Table 1 Stages of CKD based on GFR

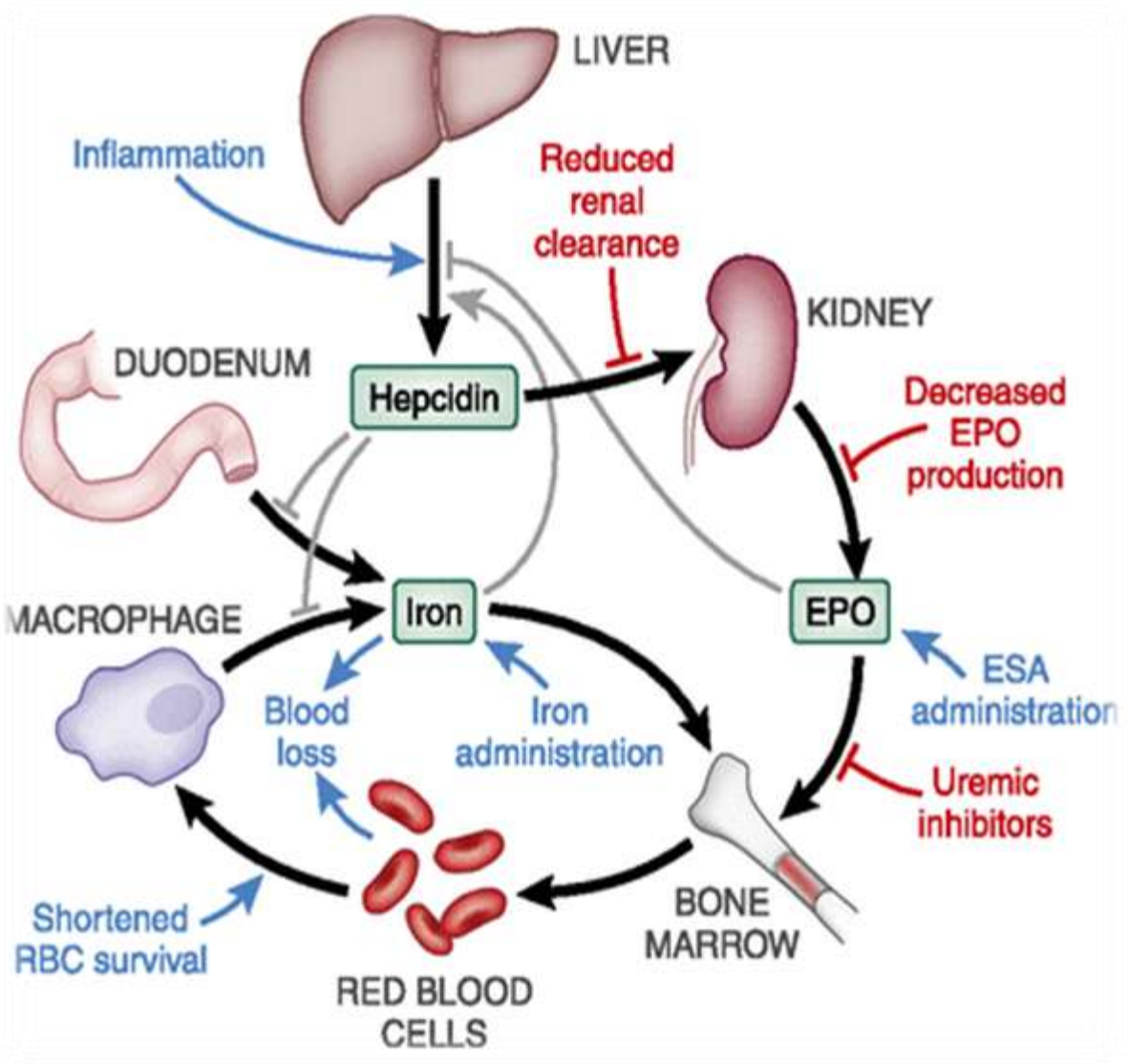

Figure 1 Mechanism of Anemia Caused by CKD

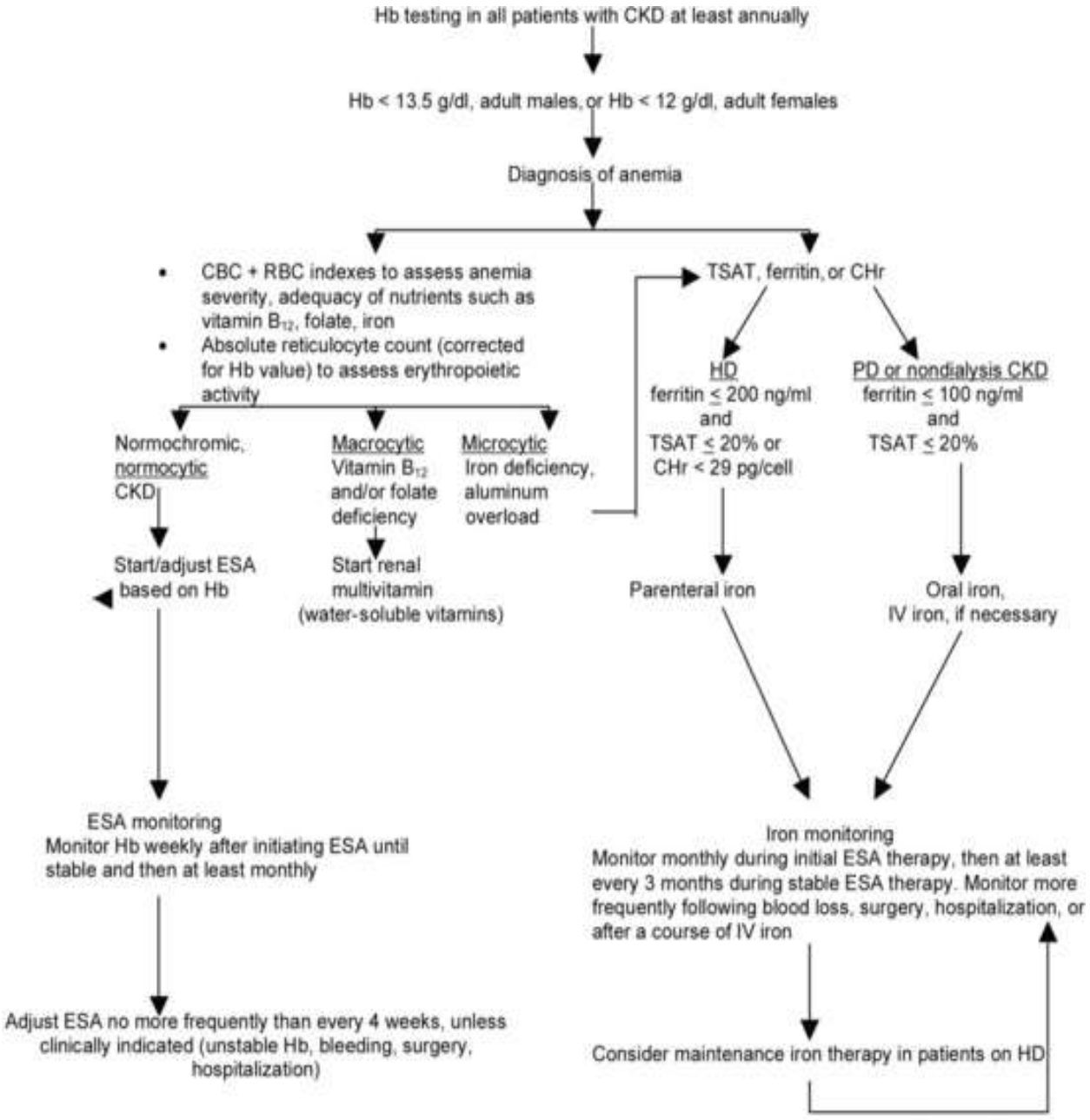

Figure 2 Treatment Options Available for Anemia due to CKD

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